

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
22 July 2004 (22.07.2004)

PCT

(10) International Publication Number
WO 2004/060882 A1

(51) International Patent Classification⁷: C07D 333/10, 213/36, 211/70, 209/44, C07C 221/27, A61K 31/137, 31/4035, 31/4418, 31/451, 31/381, A61P 25/04

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/SE2003/002088

(84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date:
29 December 2003 (29.12.2003)

Declaration under Rule 4.17:

(25) Filing Language: English

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

(26) Publication Language: English

(30) Priority Data:
0300010-6 7 January 2003 (07.01.2003) SE

Published:

(71) Applicant (for all designated States except US): AstraZeneca AB [SE/SE]; S-151 85 Södertälje (SE).

— with international search report

(72) Inventors; and

(75) Inventors/Applicants (for US only): LEUNG, Carmen [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA). TOMASZEWSKI, Miroslaw [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA). WOO, Simon [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,

WO 2004/060882 A1

(54) Title: CB 1/CB 2 RECEPTOR LIGANDS AND THEIR USE IN THE TREATMENT OF PAIN

(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable salts thereof wherein Ar₁?1, Ar₂?1, R₁?1, R₂?1, n and X are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

CB₁/CB₂ receptor ligands and their use in the treatment of pain.

BACKGROUND OF THE INVENTION

5 1. Field of the invention

The invention is related to compounds which are CB₁/CB₂ receptor ligands, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof, and more particularly to compounds that are CB₁/CB₂ receptor agonists. The present invention may also relate to compounds that may be 10 effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, vision and/or eye related disorders, gastrointestinal disorders and cardiovascular disorders.

15 2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has 20 been well known that cannabinoid receptor (e.g., CB₁ receptors, CB₂ receptors) ligands, especially agonists produce relief of pain in a variety of animal models by interacting with CB₁ and/or CB₂ receptors. Generally, CB₁ receptors are located predominately in the central nervous system, whereas CB₂ receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

25 While the conventional CB₁ receptor agonists and CB₁/CB₂ receptor agonists, such as tetrahydrocannabinol (THC) and opiate drugs, are highly effective in anti-nociception models in animals, they tend to exert many undesired CNS (central nerve system) side-effects, e.g., psychoactive side effects and the abuse potential of opiate drugs.

30 Therefore, there is a need for new CB₁/CB₂ receptor ligands such as agonists useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects. The compounds of the invention may be used to avoid the undesired CNS side effects which arise through the central CB₁ mechanism.

DISCLOSURE OF THE INVENTION

The present invention provides CB₁/CB₂ receptor ligands which are useful in treating pain and other related symptoms or diseases.

Definitions

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by reference herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

10 "CB₁/CB₂ receptors" means CB₁ and/or CB₂ receptors.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms, and having 0 to n multivalent heteroatoms selected from O, S, N and P, wherein m and n are 0 or positive integers, and n>m. For example, "C₁₋₆" would refer to a chemical group having 1 to 6 carbon atoms, and having 0 to 6 multivalent heteroatoms selected from O, S, N and P.

15 The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a 20 hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" generally includes both saturated alkyl and unsaturated alkyl.

25 The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serve to link two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon 30 double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

5 The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

10 The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms.

15 The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to links two structures together.

20 The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share 25 two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

25 The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

30 The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-

containing structure or molecule has an aromatic character (e.g., $4n + 2$ delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C₁₋₁₂hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups 5 containing one or more heteroatoms include heterocycl, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₁₂hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, 10 chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first 15 structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: 20 aziridine, oxirane, thirane, azetidine, oxetane, thietane, pyrrolidine, pyrrolidine, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, 25 homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole. 30

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline,

tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine,

5 perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle

10 includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as:

15 aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranlyl, tetrahydropyranlyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, 20 dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, 30 quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl,

phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, 5 pyrrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocycls described above, heterocyclyl includes polycyclic heterocycls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, 10 diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula -O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

15 The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula -O-Ar', wherein -Ar' is a heteroaryl.

20 The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula -NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means -C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and 25 dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

30 "RT" or "rt" means room temperature.

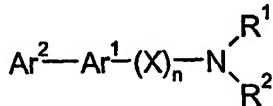
A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:

5

I

wherein

Ar¹ is arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar¹ connected to Ar² is separated from a ring atom of Ar¹ connected to X by at least one atom;

Ar² is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

n is 0 or 1;

X is a divalent group that separates groups connected thereto by one or two atoms;

R¹ is a monovalent C₁₋₂₀ group comprising one or more heteroatoms selected from S, O, N and P;

R² is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀acyl, substituted C₁₋₁₀acyl, substituted C₁₋₁₀alkyl, C₁₋₁₀alkylene, or substituted C₁₋₁₀alkylene, wherein said alkylene is linked to a ring carbon of Ar¹.

Particularly, the compounds of the present invention are those of formula I, wherein

Ar¹ is an arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar¹ connected to Ar² is separated from a ring atom of Ar¹ connected to X by at least one atom;

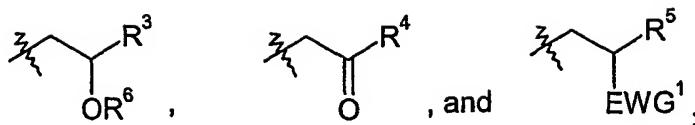
Ar² is an aryl, heteroaryl, substituted aryl or substituted heteroaryl;

X is -CH₂- or -CH₂-CH₂-;

R² is C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₁₋₃ alkylene, or substituted C₁₋₃ alkylene, wherein said alkylene is linked to a ring carbon of Ar¹.

More particularly, the compounds of the present invention are those of formula I, wherein

R¹ is selected from:



wherein R³ is optionally hydrogen, substituted C₁₋₁₀alkyl, optionally substituted C₅₋₁₂aryl, optionally substituted C₃₋₁₀heteroaryl, optionally substituted aryloxy-C₁₋₆alkyl, optionally substituted heteroaryloxy-C₁₋₆alkyl;

5 R⁴ and R⁵ are, independently, hydrogen, optionally substituted C₁₋₁₀alkyl, optionally substituted C₅₋₁₂aryl, optionally substituted C₃₋₁₀heteroaryl, amino group, -NHC(=O)-O-R⁷, or -NHC(=O)-R⁷, wherein R⁷ is C₁₋₆alkyl or aryl;

R⁶ is hydrogen, optionally substituted C₁₋₆alkyl, or optionally substituted aryl;

10 and

EWG¹ is an electron withdrawing group.

Even more particularly, the compounds of the present invention are those of formula I, wherein

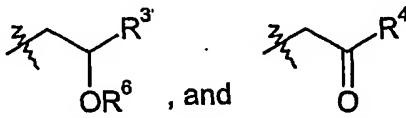
Ar¹ is optionally substituted *para*-phenylene, optionally substituted six-membered *para*-heteroarylene, or optionally substituted monocyclic five-membered *meta*-heteroarylene;

15 Ar² is optionally substituted phenyl, or optionally substituted monocyclic five or six-membered heteroaryl;

X is -CH₂-, or -CH₂-CH₂-;

20 R² is C₁₋₃ alkyl, substituted C₁₋₃ alkyl, C₁₋₃ alkylene, or substituted C₁₋₃ alkylene, wherein said alkylene is linked to a ring carbon of Ar¹.

R¹ is selected from:



wherein R³ is optionally substituted C₁₋₆alkyl, optionally substituted phenyl, optionally substituted phenoxy-methyl;

25 R⁴ is, independently, optionally substituted C₁₋₆alkyl, optionally substituted phenyl, amino, -NHC(=O)-O-R⁷, or -NHC(=O)-R⁷, wherein R⁷ is C₁₋₆alkyl or phenyl;

and

R⁶ is hydrogen, methyl or ethyl.

Most particularly, the compounds of the present invention are those of formula I, wherein

Ar¹ is *para*-phenylene or *para*-pyridylene;

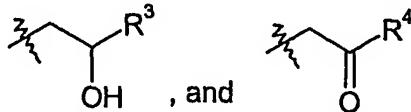
Ar² is a phenyl *ortho*-substituted with an electron withdrawing group, or a

5 thienyl *ortho*-substituted with an electron withdrawing group; Even more particularly, Ar² is a phenyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-CH(CH₃)₂, -CF₃, -NO₂, or -CN; or thienyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-CH(CH₃)₂, -CF₃, -NO₂, -CN, wherein said *ortho*-substituted Ar² is optionally further substituted at its non-*ortho* position;

10 X is -CH₂-;

R² is methyl.

R¹ is selected from:

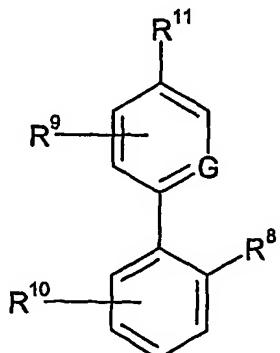


wherein R³ is optionally substituted phenyl, or optionally substituted phenoxy-15 methyl; Even more particularly, R³ is phenyl, substituted phenoxyethyl or substituted phenyl; and

R⁴ is -NHC(=O)-O-R⁷, wherein R⁷ is C₁₋₆alkyl.

In another aspect, the present invention provides a compound of formula II, or a pharmaceutically acceptable salt thereof:

20



II

wherein

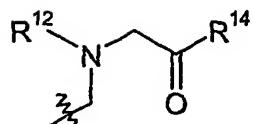
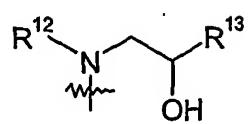
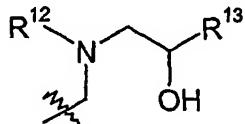
G is N or CH;

R^8 is selected from $-H$, $-CH_3$, $-CF_3$, $-NO_2$ and $-CN$;

R^9 is selected from $-H$ and C_{1-3} alkyl;

R^{10} is selected from $-H$ and C_{1-3} alkyl; and

R^{11} is selected from

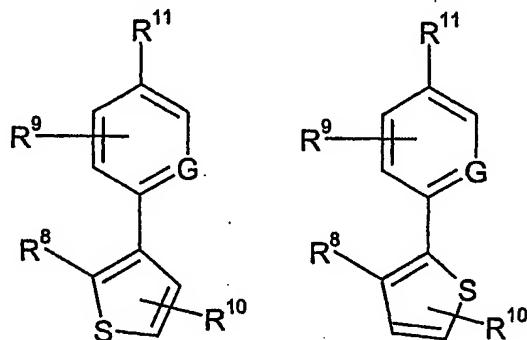


5

wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxyethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6} alkyl.

In a further aspect, the present invention provides a compound of formula III or IV, or a pharmaceutically acceptable salt thereof:

10

IIIIV

wherein

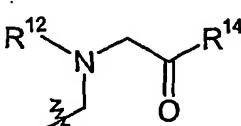
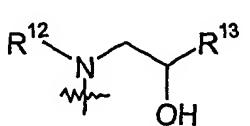
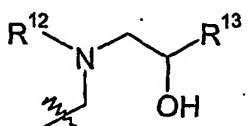
G is N or CH ;

R^8 is selected from $-H$, $-CH_3$, $-CF_3$, $-NO_2$ and $-CN$;

15 R^9 is selected from $-H$ and C_{1-3} alkyl;

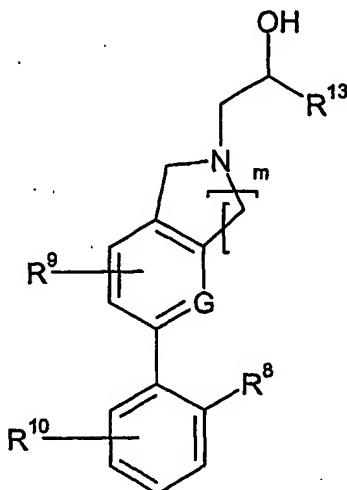
R^{10} is selected from $-H$ and C_{1-3} alkyl; and

R^{11} is selected from



20 wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxyethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6} alkyl.

In an even further aspect, the present invention provides a compound of formula V, or a pharmaceutically acceptable salt thereof:



wherein

- G is N or CH;
- m is 1 or 2;
- 10 R⁸ is selected from -H, -CH₃, -CF₃, -NO₂ and -CN;
- R⁹ is selected from -H and C₁₋₃alkyl;
- R¹⁰ is selected from -H and C₁₋₃alkyl; and
- R¹³ is phenyl or substituted phenoxyethyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I, II, III, IV or V. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present

invention includes any geometrical isomer of a compound of Formula I, II, III, IV or V. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I, II, III, IV or V.

It will also be understood that certain compounds of the present invention may 5 exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I, II, III, IV or V.

Within the scope of the invention are also salts of the compounds of the formula I, II, III, IV or V. Generally, pharmaceutically acceptable salts of compounds 10 of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt 15 by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

20 In one embodiment, the compound of formula I, II, III, IV or V above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as 25 pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB₁/CB₂ receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB₁/CB₂ receptors, and are useful in the relief of pain, particularly chronic pain, e.g., chronic inflammatory pain, neuropathic pain, back pain, cancer pain and visceral pain. 30 Compounds of the present invention will also be useful in treating acute pain. Additionally, compounds of the present invention are useful in other disease states in which degeneration or dysfunction of CB₁/CB₂ receptors is present or implicated.

Thus, the invention provides a compound of formula I, II, III, IV or V, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of 5 formula I, II, III, IV or V, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term 10 "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

15 The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical 20 composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally, intravenously or intramuscularly.

25 The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this 30 invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

5 In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

10 For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

15 The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

20 Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

25 Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

30 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

5 A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I, II, 10 III, IV or V as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I, II, III, IV or V for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I, II, III, IV or V for the manufacture of a medicament for the therapy of various pain 15 conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I, II, III, IV or V above, is administered to a 20 patient in need of such therapy.

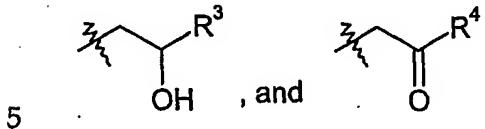
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a 25 compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, 30 in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the present invention provides a method of preparing a compound of the present invention using one or more of the general procedures

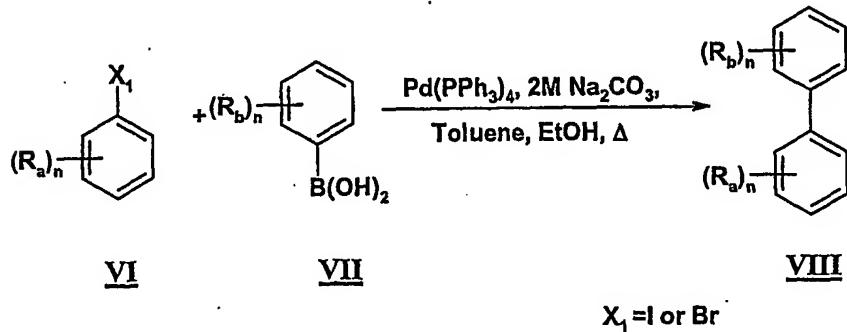
below, wherein R_a and R_b are independently selected from -H, optionally substituted C₁₋₆alkyl, optionally substituted aryl, optionally substituted heteroaryl, -CF₃, -NO₂, and -CN; n is 1 or 2; R_c, R_d, R_e and R_f are independently selected from -H, C₁₋₃alkyl,



wherein R³ is optionally substituted phenyl, or optionally substituted phenoxy-methyl;

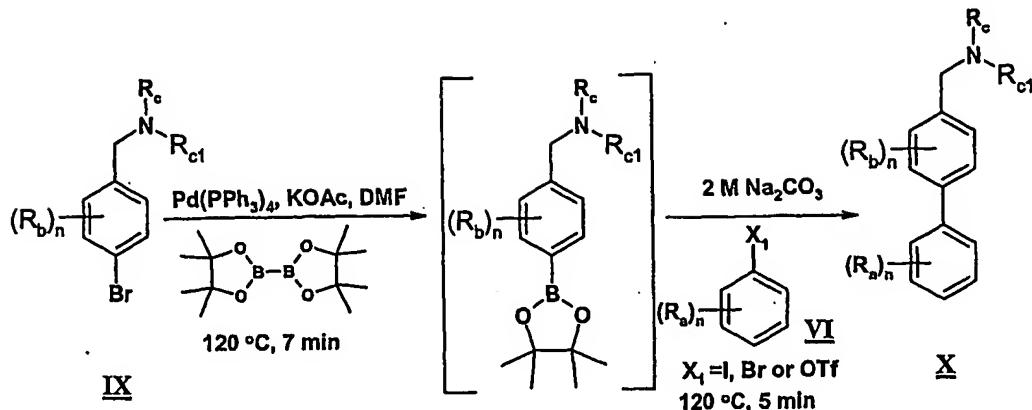
R⁴ is -NHC(=O)-O-R⁷, wherein R⁷ is C₁₋₆alkyl; R_{c1} is -H or C₁₋₃alkyl; and R_g is optionally substituted phenyl or optionally substituted phenoxy-methyl.

10 General Procedure 1:



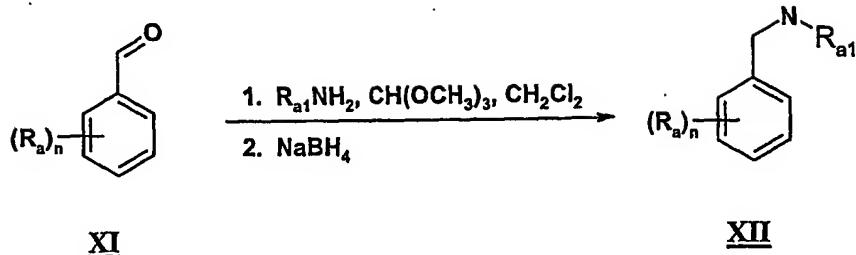
A solution of the aryl boronic acid (VII, 1.5 equiv.) in ethanol (3 mL/mmol boronic acid) was added to a mixture of the aryl halide (VI, 1 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (0.05 equiv.), toluene (9 mL/mmol aryl halide), and 2 M Na_2CO_3 (6.7 equiv.). The resulting mixture was heated at reflux until the aryl halide was consumed (typically 16 h). The reaction was then concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were then washed with brine, dried over MgSO_4 , filtered through Celite, and concentrated *in vacuo*. The residue was dissolved in methanol and allowed to stand overnight. The 15 orange solid which precipitated was filtered, and the supernatant was concentrated *in vacuo* to provide the title compound. The product (VIII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.
 20

General Procedure 2:



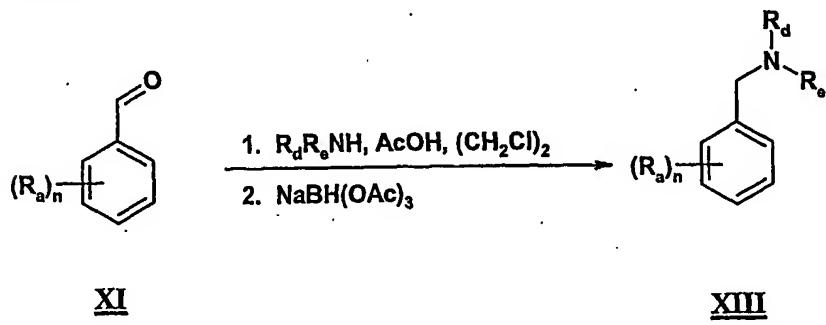
Solutions of the aryl bromide (IX, 1 equiv.) in DMF (3 mL/mmol aryl bromide) and bis(pinacolato)diboron (1.1 equiv.) in DMF (2.7 mL/mmol diboron compound) were added successively to a mixture of $\text{Pd}(\text{PPh}_3)_4$ (0.03 equiv.) and KOAc (3 equiv.) contained in a microwave process vial. The vial was capped and heated to 120 °C for 7 min using microwave irradiation. The resulting mixture was cooled, and 2 M Na_2CO_3 (4.9 equiv.) and a solution of the second aryl halide or aryl triflate (VI, 1-2 equiv.) in DMF (0.3-0.9 mL/mmol aryl halide/triflate, depending on solubility) were added to the vial through the septum cap. The reaction was heated to 120 °C for an additional 5 minutes using microwave irradiation. The resulting mixture was diluted with water (6 mL/mmol of initial aryl halide used) and CH_2Cl_2 (24 mL/mmol of initial aryl halide used), loaded onto an Extube® Chem Elut column (Varian), and eluted with two column volumes of CH_2Cl_2 . The eluant was concentrated, and the residue was dissolved in CH_2Cl_2 (12 mL/mmol of initial aryl halide used). MP-TsOH resin was added to the solution, and the mixture was stirred for 2 hours. The resin was removed by filtration and washed with additional CH_2Cl_2 and MeOH . The filtrate and washings were discarded, and the compound (X) was then released from the resin using 2M NH_3 in MeOH . The release solution was concentrated to provide the compound (X).

General Procedure 3:



A solution of $R_{41}NH_2$ in MeOH (2 M, 5 equiv.) was added to a mixture of the aldehyde (XI, 1 equiv.) and $CH(OCH_3)_3$ (10 equiv) in CH_2Cl_2 (7.5 mL/mmol aldehyde). The resulting mixture was stirred overnight at room temperature, and then $NaBH_4$ (2.5 equiv.) was added. When the starting aldehyde/intermediate imine had been completely consumed, the reaction was concentrated *in vacuo*. The residue was taken into EtOAc (10 mL/mmol aldehyde used) and the product was extracted into 1 N HCl (3 x 7.5 mL/mmol aldehyde used). The EtOAc layer was discarded, the combined aqueous layers were basicified with 6 N NaOH, and the product was back extracted with EtOAc (3 x 10 mL/mmol aldehyde used). The combined organic phases were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the compound (XII). The compound (XII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.

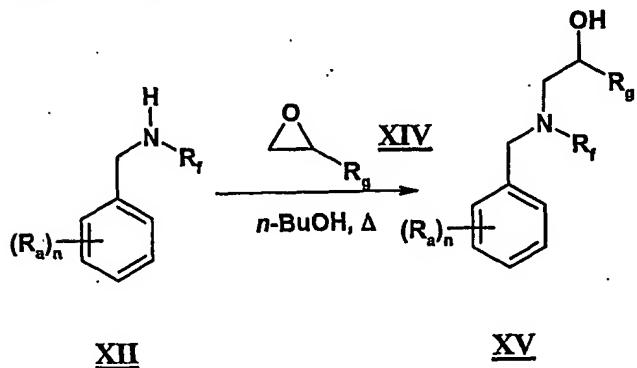
General Procedure 4:



A solution of the amine (R_dR_eNH , 1 equiv.) and aldehyde (XI, 1-2 equiv.) in
 20 AcOH/dichloroethane (5% v/v, 10 mL/mmol amine) was stirred at room temperature
 overnight. $NaBH(OAc)_3$ (2 equiv.) was then added. When the starting
 aldehyde/intermediate imine/iminium ion had been completely consumed, saturated
 Na_2CO_3 (6 mL/mmol amine) was added. The layers were separated, and the aqueous

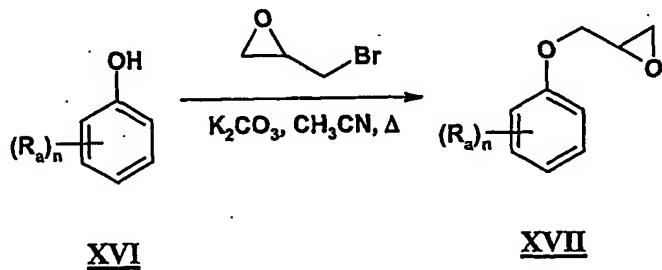
layer was extracted with additional EtOAc (3 x 12 mL/mmol amine). The combined organic phases were then dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide the compound (XIII). The compound (XIII) was used for subsequent steps, or purified by silica gel column chromatography or reverse phase HPLC when necessary.

General Procedure 5:



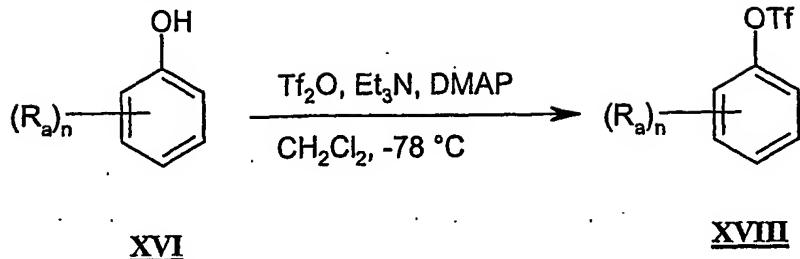
10 A solution of the amine (XII, 1 equiv.) and epoxide (XIV, 1 equiv.) in *n*-BuOH (6 mL/mmol amine) was heated at the temperature specified until the starting materials were consumed. The reaction was concentrated *in vacuo*, and the residue was purified by reverse phase HPLC to provide the compound (XV).

15 General Procedure 6:



20 A suspension of the phenol (XVI, 1 equiv.), epibromohydrin (5 equiv.), and K₂CO₃ (5 equiv.) in dry CH₃CN (8 mL/mmol phenol) was heated at 70 °C until the starting phenol was completely consumed (typically 16 h). The reaction mixture was filtered to remove solids which were then washed with additional CH₃CN. The filtrate was concentrated to provide the compound (XVII).

General Procedure 7:



5 Triethylamine (2.2 equiv.), followed by triflic anhydride (1.1 equiv.), was
 added dropwise to a solution of the phenol (XVI, 1 equiv.) and DMAP (0.1 equiv.) in
 dry CH_2Cl_2 (10 mL/mmol phenol) maintained at -78°C . The reaction was allowed to
 slowly warm to room temperature and stirred until the starting phenol was completely
 consumed (typically 16 h). Once the reaction was complete, water was added (10
 10 mL/mmol phenol), the layers were separated, and the aqueous phase was extracted
 with CH_2Cl_2 (2 x 10 mL/mmol phenol). The combined organic phases were then
 dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Silica gel column
 chromatography on the organic phase residue provided the compound (XVIII).

The compounds of the invention were found to be active towards CB₁/CB₂ receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention have been found to be effective CB₁/CB₂ receptor agonists. *In vitro* assays, *infra*, demonstrated these surprising activities. In these *in vitro* assays, a compound is tested for their activity toward CB₁/CB₂ receptors and the dissociation constant (K_i) is obtained to determine the selective activity for a particular compound towards CB₁/CB₂ receptors by measuring IC₅₀ of the compound. In the current context, IC₅₀ generally refers to the concentration of the compound at which 50% displacement of a standard radioactive CB₁/CB₂ receptor ligand has been observed. Generally, a lower K_i for a particular compound towards CB₁/CB₂ receptors means that the particular compound is a stronger ligand towards the CB₁/CB₂ receptors. As a result, compounds with relatively low K_i towards CB₁/CB₂ receptors are relatively strong CB₁/CB₂ receptor ligands or strong CB₁/CB₂ receptor agonists.

Biological Evaluation

hCB₁ and hCB₂ receptor binding

Human CB₁ receptor from Receptor Biology (hCB1) or human CB₂ receptor from BioSignal (hCB2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM MgCl₂, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC₅₀ of the compounds of the invention at hCB₁ and hCB₂ are evaluated from 10-point dose-response curves done with ³H-CP55,940 at 20000 to 25000 dpm per well (0.17-10 0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM MgCl₂, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$$20 \quad Ki = IC_{50}/(1+[rad]/Kd),$$

Wherein IC₅₀ is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

25 Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

Biological data for certain compounds of the invention are listed in Table 1 below.

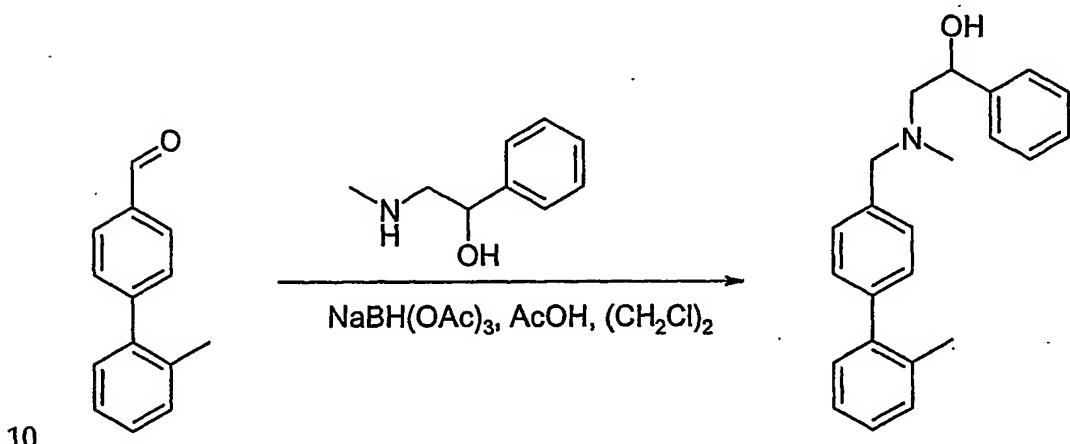
Table 1

Compound No.	CB ₂ (Ki, nM)	CB ₁ (Ki, nM)
1-132	15-2800	50-5000

EXAMPLES

The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may 5 be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1: α -[[Methyl[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol

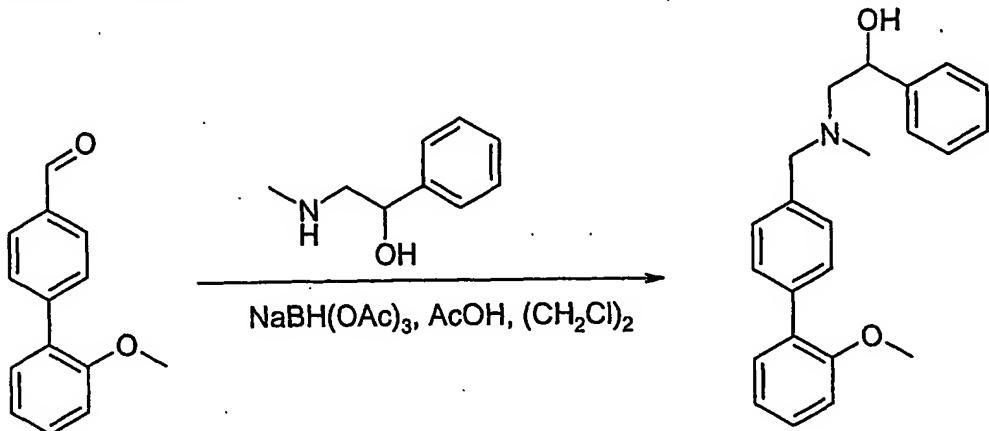


Following General Procedure 4, 2'-methyl-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.28 mmol), α -[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and NaBH(OAc)₃ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) 15 was added. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH₂Cl₂. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH₃CN in H₂O) to provide the title compound (0.052 g, 11%) as its HCO₂H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CDCl₃): δ 7.39-7.23 (br m, 13H), 4.83 (dd, *J*=3.8 Hz, *J*=10.2 Hz, 1H), 3.94-3.85 (overlapping br s at 3.94 and d at 3.87, *J*=13.2 Hz, 2H), 3.68 (d, *J*=12.8 Hz, 1H), 2.72 (dd, *J*=10.0 Hz, *J*=12.4 Hz, 1H), 2.63 (dd, *J*=3.6 Hz, *J*=12.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H). MS (ESI) (M+H)⁺ = 332. Anal. Calcd for C₂₃H₂₅NO + 0.30 CH₂O₂: C, 81.06; H, 7.47; N, 4.06. Found: C, 81.40; H, 7.76; N, 4.18.

20

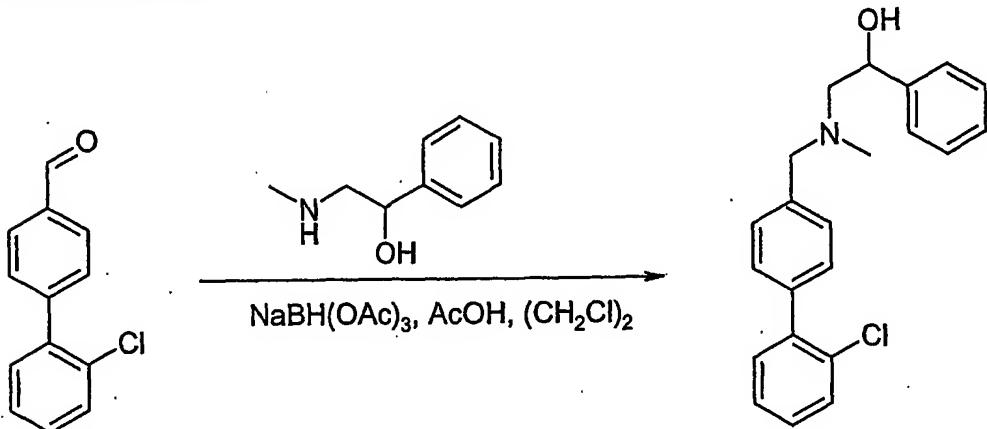
25

Example 2: α -{[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl}-benzenemethanol



Following General Procedure 4, 2'-methoxy-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.18 mmol), α -[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH_2Cl_2 . The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.048 g, 10%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $^1\text{H-NMR}$ (CDCl_3): δ 7.54 (d, $J=8.4$ Hz, 2H), 7.40-7.25 (br m, 9H), 7.05-6.98 (m, 2H), 4.88 (dd, $J=2.6$ Hz, $J=10.2$ Hz, 1H), 4.55 (br s, 1H), 3.91 (d, $J=13.6$ Hz, 1H), 3.81-3.74 (overlapping s at 3.81 and d at 3.75, $J=13.2$ Hz, 4H), 2.79 (dd, $J=10.0$ Hz, $J=13.2$ Hz, 1H), 2.68 (dd, $J=3.2$ Hz, $J=12.8$ Hz, 1H), 2.48 (s, 3H). MS (ESI) ($\text{M}+\text{H}^+$) = 348. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_2 + 0.40 \text{CH}_2\text{O}_2$: C, 76.82; H, 7.11; N, 3.83. Found: C, 76.98; H, 7.17; N, 3.77.

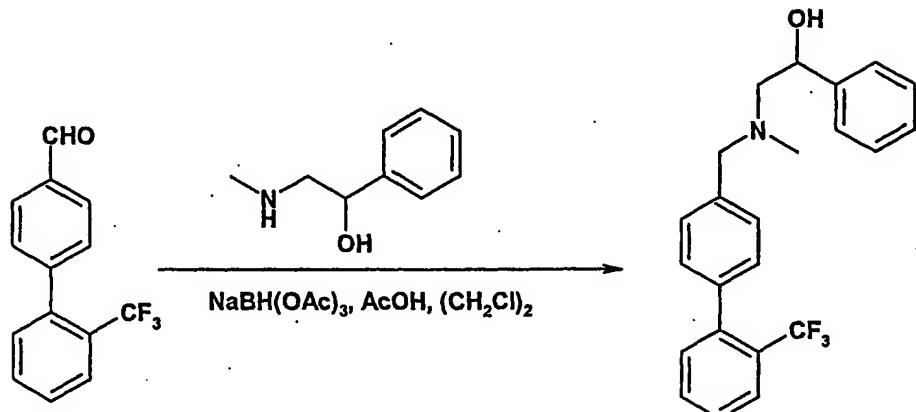
Example 3: α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol



Following General Procedure 4, 2'-chloro-[1,1'-biphenyl]-4-carboxaldehyde

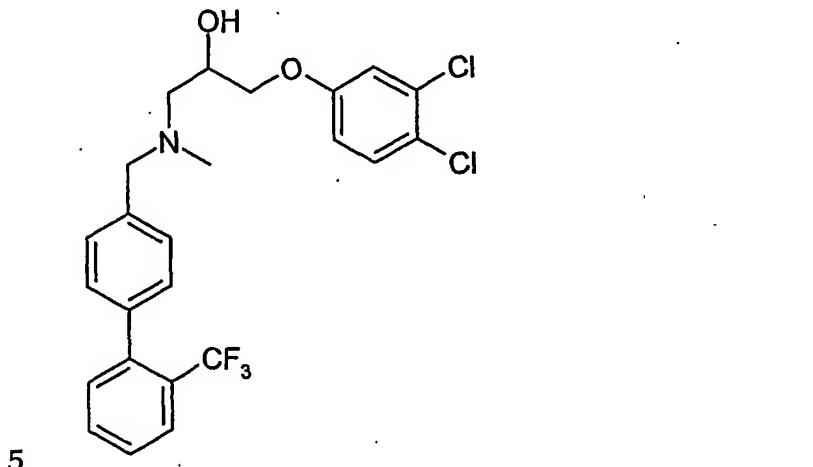
5 (0.250 g, 1.16 mmol), α -[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and NaBH(OAc)₃ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmole amine) was added. The layers were then filtered through a Hydromatix® column and the product was eluted with CH₂Cl₂. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH₃CN in H₂O) to provide the title compound (0.050 g, 11%) as its HCO₂H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CDCl₃): δ 7.49-7.26 (br m, 13H), 4.85 (dd, *J*=3.2 Hz, *J*=10.8 Hz, 1H), 4.18 (br s, 1H), 3.89 (d, *J*=12.8 Hz, 1H), 3.72 (d, *J*=13.2 Hz, 1H), 2.75 (dd, *J*=10.4 Hz, *J*=12.8 Hz, 1H), 2.65 (dd, *J*=3.2 Hz, *J*=12.8 Hz, 1H), 2.46 (s, 3H). MS (ESI) (M+H)⁺ = 352. Anal. Calcd for C₂₂H₂₂NOCl + 0.30 CH₂O₂: C, 73.25; H, 6.23; N, 3.83. Found: C, 73.44; H, 6.31; N, 3.86.

Example 4: α -[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

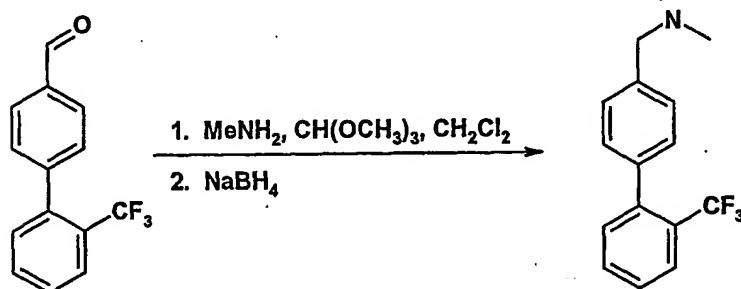


Following General Procedure 4, 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (0.500 g, 2.00 mmol), α -[(methylamino)methyl]benzenemethanol (0.604 g, 4.00 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.844 g, 4.00 mmol) were combined. The crude product was purified by flash chromatography (3:7 Hexanes:EtOAc) to provide the title compound. HCl in Et_2O (2 mL of 1M, 2.00 mmol) was added to the compound and the resulting solid was filtered and washed with additional Et_2O to provide the HCl salt (0.558 g, 66%). Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $^1\text{H-NMR}$ (CD_3OD): δ 7.81 (d, $J=7.6$ Hz, 1H), 7.71-7.56 (m, 4H), 7.52-7.32 (m, 8H), 5.15-5.09 (m, 1H), 4.77 (br d, $J=14.0$ Hz, 0.5H), 4.50 (AB_q, 1H), 4.33 (br d, $J=12.0$ Hz, 0.5H), 3.46-3.15 (m, 2H), 3.08 (s, 1.5H), 2.92 (s, 1.5H). MS (ESI) ($\text{M}+\text{H}$)⁺ = 386. Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{F}_3\text{NO}+1.1 \text{ HCl}$: C, 64.92; H, 5.47; N, 3.29. Found: C, 65.16; H, 5.63; N, 3.37.

Example 5: 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol

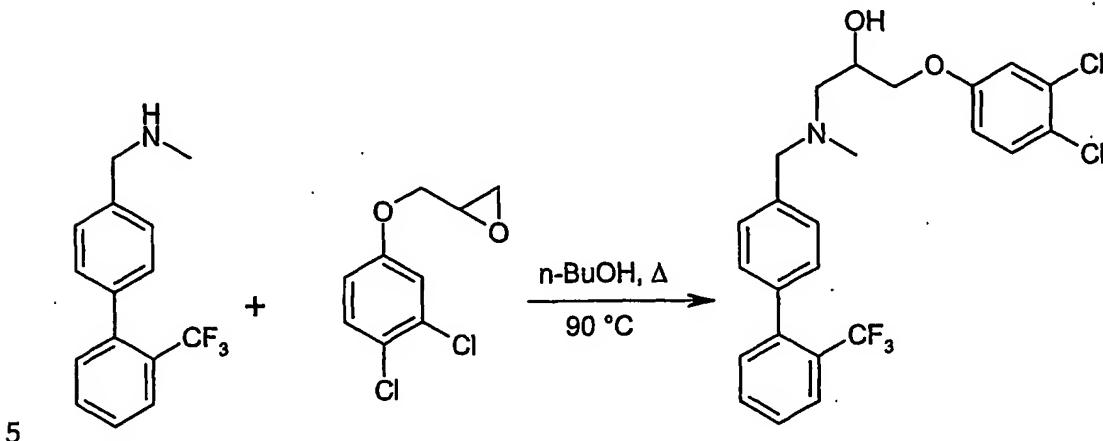


Compound 5A: *N*-Methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine



Following General Procedure 3, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.400 g, 1.60 mmol) was converted to the title compound (0.297 g, 10 70%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. $^1\text{H-NMR}$ (CDCl_3) δ 7.75 (d, $J=7.6$ Hz, 1H), 7.56 (t, $J=7.2$ Hz, 1H), 7.46 (d, $J=7.6$ Hz, 1H), 7.42-7.28 (m, 5H), 3.82 (s, 2H), 2.51 (s, 3H), 2.13 (br s, 1H). MS (ESI) $(\text{M}+\text{H})^+ = 266$.

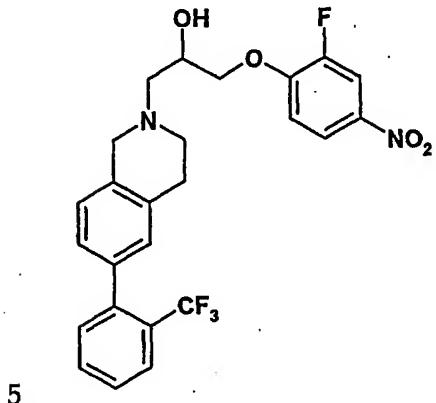
Compound 5b: 1-(3,4-Dichlorophenoxy)-3-[methyl[(2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol



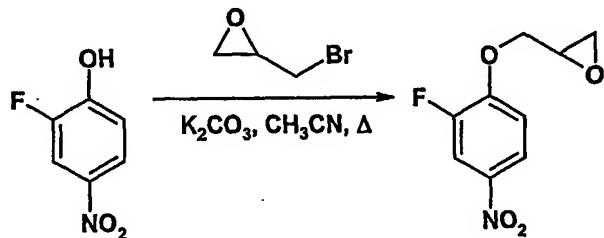
Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.133 g, 0.40 mmol) and 2-[3,4-dichlorophenoxy)methyl]oxirane (0.088 g, 0.40 mmol) were combined and heated at 50°C for 24 h. The crude product 10 was purified by reverse phase HPLC (gradient 30-70% CH₃CN in H₂O) to provide the title compound (0.026 g, 11%) as its TFA salt. This material was lyophilized from H₂O/CH₃CN to produce a white solid. ¹H-NMR (CDCl₃): δ 7.77 (d, *J*=7.6 Hz, 1H), 7.60 (t, *J*=7.4 Hz, 1H), 7.53-7.51 (m, 3H), 7.43 (d, *J*=8.0 Hz, 2H), 7.34-7.31 (overlapping s at 7.33 and d at 7.32, *J*=8.8 Hz, 2H), 6.97 (d, *J*=2.8 Hz, 1H), 6.73 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 1H), 4.50 (br s, 1H), 4.36 (br s, 2H), 4.07 (br s, 1H), 3.89 (t, *J*=8.2 Hz, 1H), 3.51-3.03 (br s at 3.36 and br s at 3.16, 2H), 2.94 (br s, 3H). MS (ESI) (M+H)⁺ = 484. Anal. Calcd for C₂₄H₂₂Cl₂F₃NO₂ + 0.3 H₂O + 0.9 TFA: C, 52.31; H, 4.00; N, 2.36. Found: C, 52.32; H, 3.93; N, 2.24.

15

Example 6: α -[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



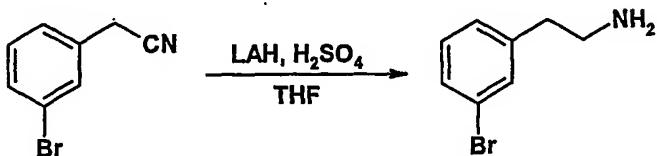
Compound 6a: 2-[(2-Fluoro-4-nitrophenoxy)methyl]oxirane



Following General Procedure 6, 2-fluoro-4-nitrophenol (0.471 g, 3.00 mmol) 10 was converted to the title compound (0.635 g, 99%). The crude compound was used for subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 8.06 (ddd, $J=1.2$ Hz, $J=2.4$ Hz, $J=8.8$ Hz, 1H), 8.00 (dd, $J=2.4$ Hz, $J=10.4$ Hz, 1H), 7.10 (dd, $J=8.0$ Hz, $J=9.2$ Hz, 1H), 4.48 (dd, $J=2.4$ Hz, $J=11.2$ Hz, 1H), 4.11 (dd, $J=6.0$ Hz, $J=11.6$ Hz, 1H), 3.45-3.39 (m, 1H), 2.97 (dd, $J=4.0$ Hz, $J=4.8$ Hz, 1H), 2.81 (dd, $J=2.8$ Hz, $J=4.8$ Hz, 1H).

15

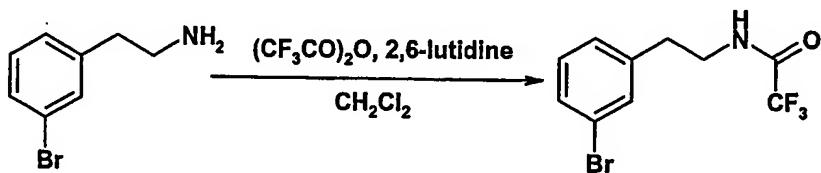
Compound 6b: 3-Bromobenzeneethanamine



A suspension of LiAlH₄ (1.24 g, 32.7 mmol) in dry THF (50 mL) was cooled to 0 °C. Concentrated H₂SO₄ (1.6 g, 16.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. A solution of 3-bromo-
 benzeneacetonitrile (4.01 g, 20.4 mmol) in THF (5 mL) was added dropwise, and the
 5 reaction was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 1 h, and then cooled back to 0 °C and quenched by the addition of a 1:1 THF:H₂O mixture (5 mL). Et₂O was added (20 mL), followed by a 3.6 M solution of NaOH (10 mL). The mixture was filtered through Celite, and the solids were washed well with additional Et₂O. The organic
 10 phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide the title compound (3.91 g, 96%). The crude compound was used in subsequent steps. ¹H-NMR (CDCl₃): δ 7.38-7.30 (overlapping s at 7.35 and d, *J*=7.2 Hz for d, 2H), 7.20-7.10 (m, 2H), 2.96 (t, *J*=6.8 Hz, 2H), 2.72 (t, *J*=6.4 Hz, 2H), 1.35 (br s, 2H). MS (ESI) (M+H)⁺ = 200/202.

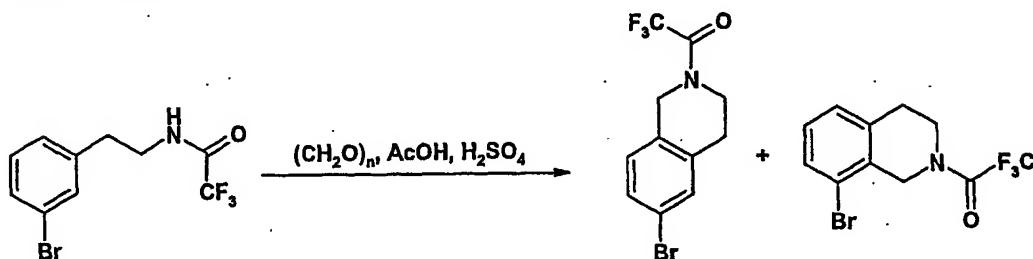
15

Compound 6c: *N*-[2-(3-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide



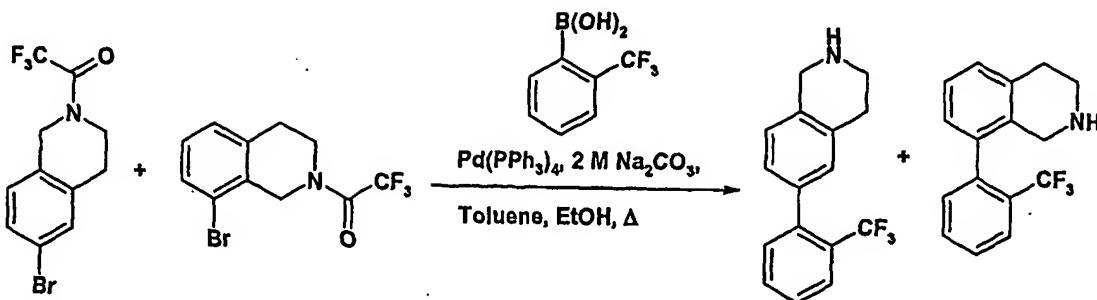
A mixture of 3-bromobenzeneethanamine (2.00 g, 10.0 mmol) and 2,6-lutidine (1.2 mL, 10.3 mmol) in dry CH₂Cl₂ (40 mL) was cooled to 0 °C. Trifluoroacetic
 20 anhydride (1.4 mL, 9.9 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (40 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 40 mL). The combined organic phases were washed successively with 1 M HCl (40 mL) and saturated NaHCO₃ (40 mL), and then dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide the title compound (2.93 g, 100%). The crude compound was used in subsequent steps. ¹H-NMR (CDCl₃): δ 7.40 (d, *J*=8.0 Hz, 1H), 7.36 (s, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.12 (d, *J*=7.6 Hz, 1H), 6.33 (br s, 1H), 3.59 (q, *J*=6.8 Hz, 2H), 2.87 (t, *J*=7.2 Hz, 2H). MS (ESI) (M+H)⁺ = 296/298.

5 **Compound 6d: 6-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline**



A mixture of glacial acetic acid (22.5 mL) and concentrated sulfuric acid (15 mL) was added to a mixture of *N*-[2-(3-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (4.06 g, 13.7 mmol) and paraformaldehyde (0.659 g, 22.0 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 16 h, and then poured into 300 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with saturated NaHCO₃ (3 x 100 mL) and water (2 x 150 mL). The organic phase was then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide a mixture of the title compounds (3.31 g, 78%). Due to hindered rotation about the amide bond, rotamers were observed in the ¹H-NMR spectrum. ¹H-NMR (CDCl₃): δ 7.46 (dd, *J*=2.0 Hz, *J*=6.8 Hz, 0.33H), 7.38-7.31 (m, 1.33H), 7.15-7.09 (m, 0.67H), 7.05-6.98 (m, 0.67H), 4.75, 4.73, 4.69 (3 x s, 2H), 3.90-3.80 (m, 2H), 3.00-2.90 (m, 2H). MS (ESI) (M+H)⁺ = 308/310.

25 **Compound 6e: 1,2,3,4-Tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline and 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline**

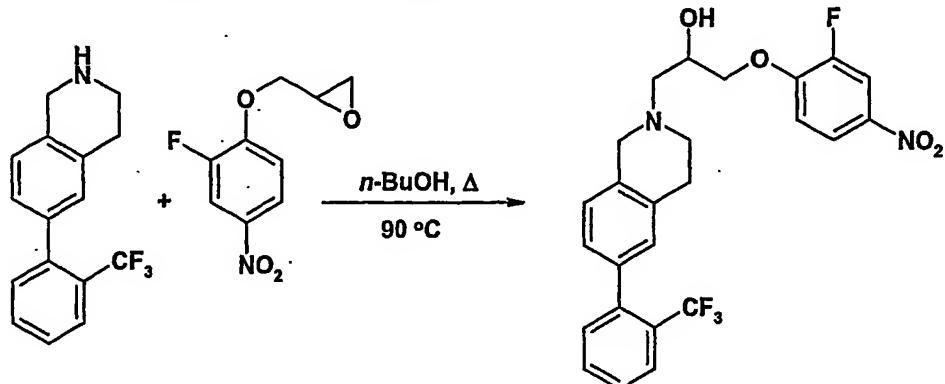


Following General Procedure 1, a mixture of 6-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline (0.137 g, 0.446 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.127 g, 0.668 mmol) to provide a mixture of the title compounds. Purification by column chromatography (4:1 CH₂Cl₂:MeOH + 0.1% conc. NH₃) provided 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline (0.0380 g, 31%) and 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline (0.0810 g, 65%).

1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline: ¹H-NMR (CDCl₃): δ 7.77 (d, *J*=7.2 Hz, 1H), 7.56 (t, *J*=7.6 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.16 (d, *J*=6.8 Hz, 1H), 7.01 (d, *J*=7.6 Hz, 1H), 4.66 (br s, 1H), 3.72 (half of br AB_q, *J*=16.0 Hz, 1H), 3.57 (half of br AB_q, *J*=15.6 Hz, 1H), 3.19 (br s, 2H), 2.97 (br s, 2H). MS (ESI) (M+H)⁺ = 278.

1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline: ¹H-NMR (CDCl₃): δ 7.74 (d, *J*=7.6 Hz, 1H), 7.55 (t, *J*=6.8 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.07 (s, 1H), 7.06 (d, *J*=8.0 Hz, 1H), 4.12 (br s, 2H), 3.87 (br s, 1H), 3.23 (br s, 2H), 2.88 (br s, 2H). MS (ESI) (M+H)⁺ = 278.

Compound 6f: α -[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



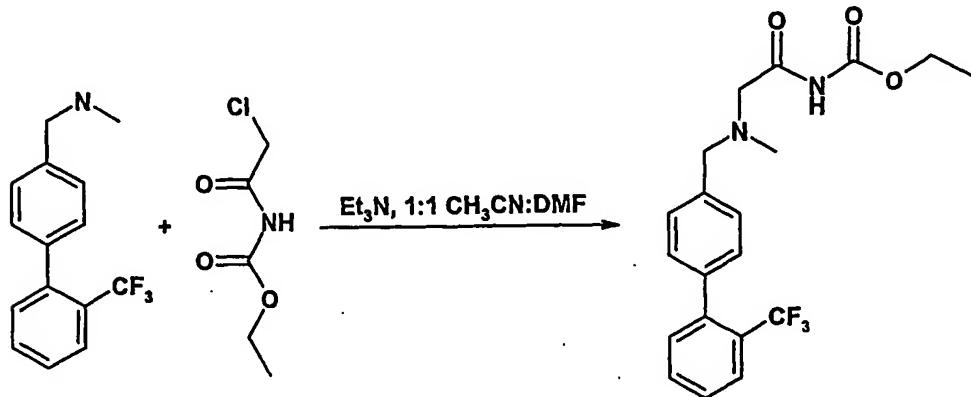
Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-

5 (trifluoromethyl)phenyl]-isoquinoline (0.0256 g, 0.0923 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0197 g, 0.0924 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to provide the title compound (0.0222 g, 40%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile to produce a white, hygroscopic

10 solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 8.15-8.11 (m, 1H), 8.08 (dd, J=2.8 Hz, J=11.2 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.57 (t, J=7.6 Hz, 1H), 7.39-7.24 (m, 5H), 4.82-4.50 (br m, 3H), 4.29 (d, J=4.8 Hz, 2H), 3.95 (br s, 1H), 3.62-3.52 (m, 3H), 3.38-3.22 (br m, 2H). MS (ESI) (M+H)⁺ = 491. Anal.

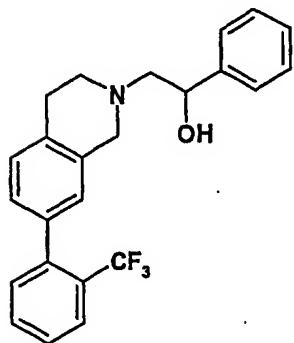
15 Calcd for C₂₅H₂₂F₄N₂O₄+1.1 TFA+0.7 H₂O: C, 51.98; H, 3.93; N, 4.46. Found: C, 52.02; H, 3.93; N, 4.42.

Example 7: Ethyl [[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]-acetyl]carbamate



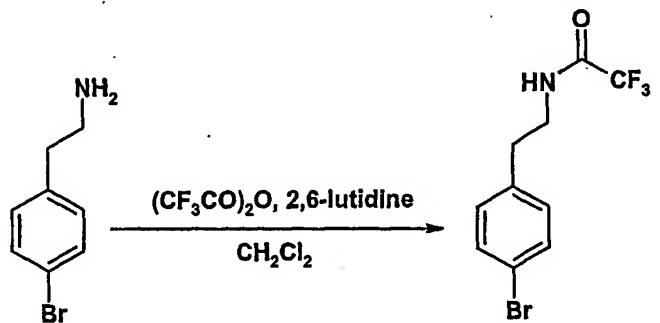
A mixture of N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine
 5 (0.0781 g, 0.294 mmol), ethyl N-(chloroacetyl)carbamate (0.0487 g, 0.294 mmol),
 and triethylamine (0.041 mL, 0.29 mmol) in 1:1 CH₃CN:DMF (3 mL) was stirred at
 room temperature for 24 h. The reaction mixture was concentrated, and the residue
 was partitioned between CH₂Cl₂ (5 mL) and H₂O (5 mL). The phases were separated,
 and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic
 10 phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude
 product was purified by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to
 provide the title compound (0.0992 g, 86%) as its TFA salt. This material was
 lyophilized from H₂O/acetonitrile. ¹H-NMR (CD₃OD): δ 7.81 (d, *J*=8.0 Hz, 1H), 7.68
 (t, *J*=7.6 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 2H), 7.59 (t, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.0 Hz,
 15 2H), 7.38 (d, *J*=7.6 Hz, 1H), 4.70-4.30 (br, 3H), 4.24 (q, *J*=7.2 Hz, 2H), 2.95 (s, 3H),
 1.31 (t, *J*=7.2 Hz, 3H). MS (ESI) (M+H)⁺ = 395. Anal. Calcd for C₂₀H₂₁F₃N₂O₃+1.3
 TFA+0.4 H₂O: C, 49.37; H, 4.23; N, 5.09. Found: C, 49.45; H, 4.23; N, 5.05.

Example 8: 3,4-Dihydro- α -phenyl-7-[2-(trifluoromethyl)phenyl]-2(1H)-isoquinolineethanol



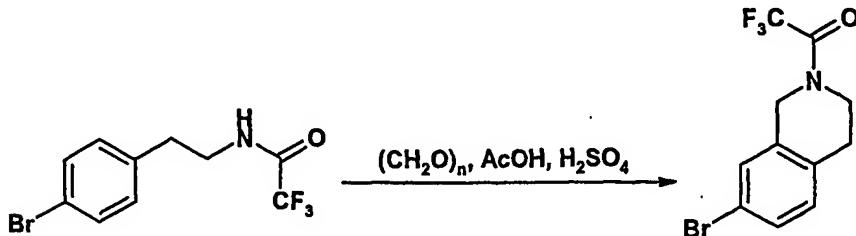
5

Compound 8a: *N*-[2-(4-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide



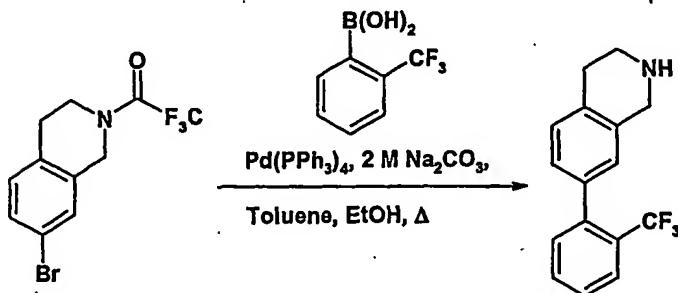
A mixture of 4-bromobenzeneethanamine (1.23 g, 6.17 mmol) and 2,6-lutidine (0.76 mL, 6.5 mmol) in dry CH_2Cl_2 (25 mL) was cooled to 0 °C. Trifluoroacetic anhydride (0.87 mL, 6.2 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (25 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were washed successively with 1 M HCl (25 mL) and saturated NaHCO_3 (25 mL), and then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the title compound (1.79 g, 98%). The crude compound was used in subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 7.49-7.45 (m, 2H), 7.10-7.06 (m, 2H), 6.27 (br s, 1H), 3.61 (q, $J=6.8$ Hz, 2H), 2.86 (t, $J=6.8$ Hz, 2H). MS (ESI) ($\text{M}+\text{H}$)⁺ = 296/298.

Compound 8b: 7-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline



A mixture of glacial acetic acid (5.1 mL) and concentrated sulfuric acid (3.4 mL) was added to a mixture of *N*-[2-(4-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (0.903 g, 5.05 mmol) and paraformaldehyde (0.147 g, 4.88 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 20 h, and then poured into 65 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with saturated NaHCO₃ (16 mL) and water (2 x 35 mL), and then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound (0.885 g, 94%) as a colorless oil. Due to hindered rotation about the amide bond, rotamers were observed in the ¹H-NMR spectrum. ¹H-NMR (CDCl₃): δ 7.38-7.27 (m, 2H), 7.06 (d, *J*=9.6 Hz, 0.36H), 7.04 (d, *J*=8.4 Hz, 0.64H), 4.76 (s, 1.3H), 4.71 (s, 0.7H), 3.88 (t, *J*=6.4 Hz, 0.7H), 3.84 (t, *J*=6.4 Hz, 1.3H), 2.91 (t, *J*=5.6 Hz, 1.3H), 2.90 (t, *J*=6.4 Hz, 0.7H). MS (ESI) (M+H)⁺ = 308/310.

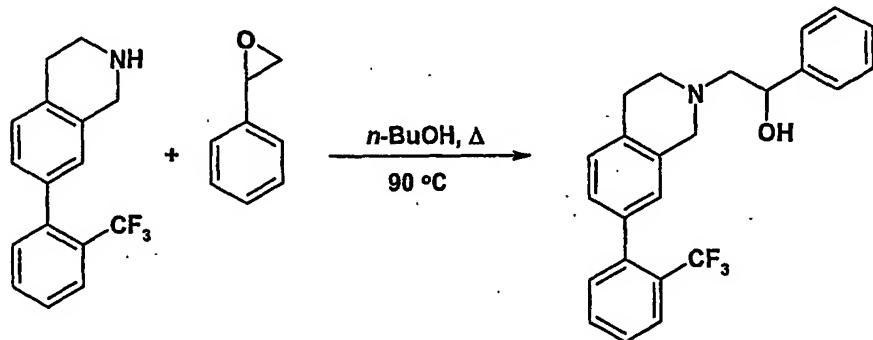
Compound 8c: 1,2,3,4-Tetrahydro-7-[2-(trifluoromethyl)phenyl]isoquinoline



Following General Procedure 1, 7-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline (0.468 g, 1.52 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.433 g, 2.28 mmol) to provide the title compound (0.387 g, 92%) following purification by column chromatography (85:15 CH₂Cl₂:MeOH + 0.1% conc. NH₃). ¹H-NMR (CDCl₃): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.54

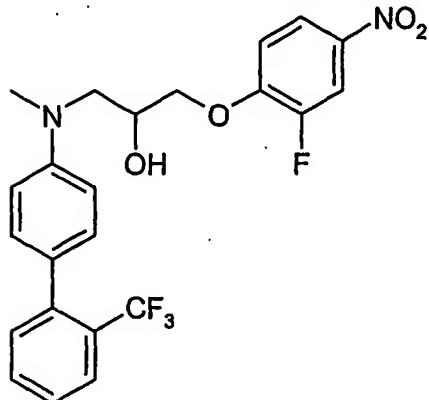
(t, $J=7.6$ Hz, 1H), 7.45 (t, $J=8.0$ Hz, 1H), 7.31 (d, $J=7.6$ Hz, 1H), 7.12 (collapsed AB_q, 2H), 6.99 (s, 1H), 4.05 (s, 2H), 3.20 (t, $J=5.6$ Hz, 2H), 2.86 (t, $J=6.0$ Hz, 2H), 2.43 (br s, 1H). MS (ESI) ($M+H$)⁺ = 278.

5 **Compound 8d: 3,4-Dihydro- α -phenyl-7-[2-(trifluoromethyl)phenyl]-2(1H)-isoquinolineethanol**

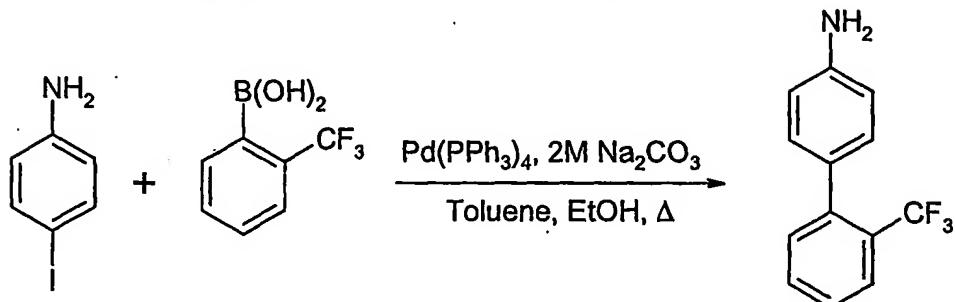


Following General Procedure 5, 1,2,3,4-tetrahydro-7-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0509 g, 0.184 mmol) and 2-(phenyl)oxirane (0.021 mL, 0.0877 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to provide the title compound (0.0138 g, 15%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.80 (d, $J=8.0$ Hz, 1H), 7.67 (t, $J=7.6$ Hz, 1H), 7.57 (t, $J=7.6$ Hz, 1H), 7.53-7.47 (m, 2H), 7.44-7.32 (m, 5H), 7.29 (d, $J=8.4$ Hz, 1H), 7.27-7.14 (br m, 1H), 5.25 (dd, $J=3.6$ Hz, $J=10.4$ Hz, 1H), 4.88-4.43 (br m, 2H), 4.13-3.90 (br m, 1H), 3.62-3.14 (br m, 5H). MS (ESI) ($M+H$)⁺ = 398. Anal. Calcd for C₂₄H₂₂F₃NO+1.1 TFA: C, 60.19; H, 4.45; N, 2.68. Found: C, 60.16; H, 4.38; N, 2.61.

Example 9: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol



Compound 9a: 2'-(Trifluoromethyl)- [1,1'-biphenyl]-4-amine

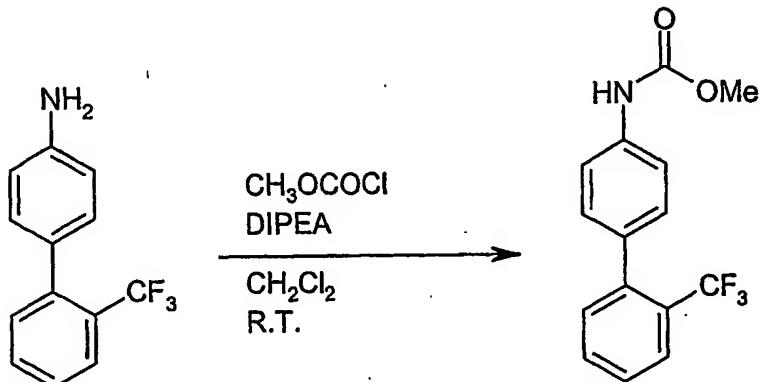


5

Following General Procedure 1, 4-iodoaniline(1.00 g, 4.57 mmol), 2-(trifluoromethyl)phenylboronic acid (1.302 g, 6.86 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.265 g, 0.23 mmol), and 2 M Na_2CO_3 (16 mL, 32 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound (0.476 g, 44%). $^1\text{H-NMR}$ (CDCl_3): δ 7.71 (dd, $J=0.4$ Hz, $J=7.8$ Hz, 1H), 7.52 (t, $J=7.4$ Hz, 1H), 7.41 (t, $J=7.8$ Hz, 1H), 7.32 (dd, $J=0.4$ Hz, $J=7.6$ Hz, 1H), 7.12 (d, $J=8.2$ Hz, 1H), 6.73-6.69 (m, 2H), 3.73 (br s, 2H). MS (ESI) $(\text{M}+\text{H})^+ = 238$.

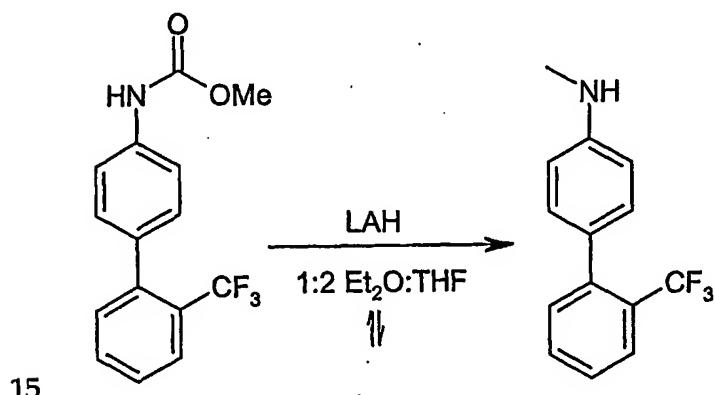
15

Compound 9b: Methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate



To a solution of 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (0.476 g, 2.01 mmol) and DIPEA (0.45 mL, 2.61 mmol) in CH_2Cl_2 (4.5 mL) maintained at 0 °C was added 5 methylchloroformate (0.17 mL, 2.21 mmol). The reaction was allowed to slowly warm to room temperature, stirred overnight, diluted with CH_2Cl_2 (15 mL), and washed with 1 N HCl (2 x 20 mL) and brine (1 x 20 mL). The organic layer was then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the title compound (0.563 g, 95%) as a beige solid. $^1\text{H-NMR}$ (CDCl_3): δ 7.74 (dd, $J=0.6$ Hz, $J=7.8$ Hz, 1H), 7.50 (t, $J=7.8$ Hz, 1H), 7.47-7.42 (overlapping d and t, $J=8.0$ Hz for d and $J=8.4$ Hz for t, 3H), 7.32 (d, $J=8.0$ Hz, 1H), 7.28 (d, $J=8.4$ Hz, 2H), 6.69 (br s, 1H), 3.80 (s, 3H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 296$.

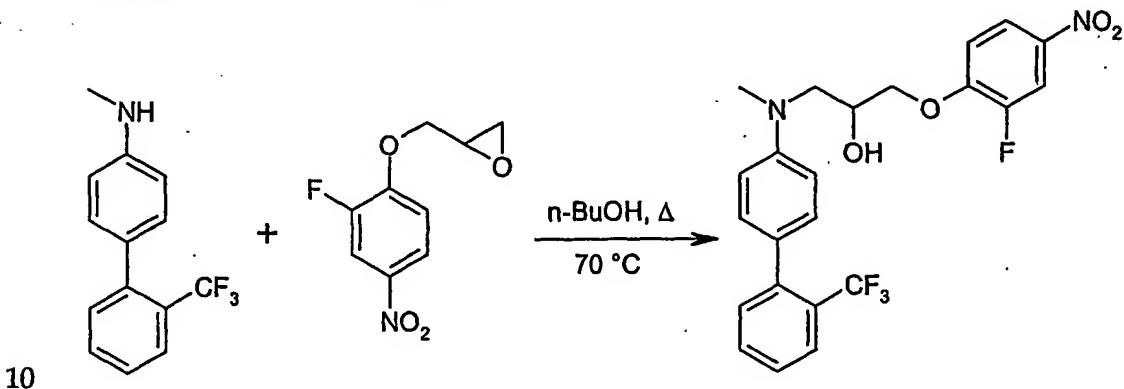
Compound 9c: N-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine



15 To a solution of methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate (0.554 g, 1.88 mmol) in 1:2 dry $\text{Et}_2\text{O}:\text{THF}$ (30 mL) was added LAH in Et_2O (2.82 mL, 2.82 mmol) dropwise. The reaction was refluxed for 4 hrs, cooled down to room

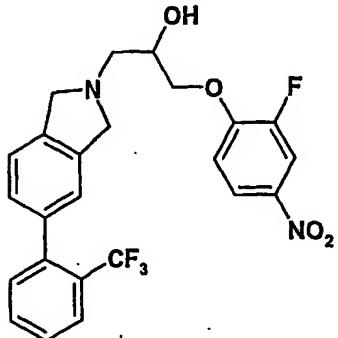
temperature, diluted with Et_2O (40 mL), and quenched with $\text{Na}_2\text{SO}_4 \cdot 5\text{H}_2\text{O}$ (2 g). The reaction mixture was stirred until the solution turned clear, filtered, and concentrated *in vacuo* to provide the title compound (0.409 g, 87%) as a yellow oil. $^1\text{H-NMR}$ (CDCl_3): δ 7.71 (d, $J=8.2$ Hz, 1H), 7.52 (t, $J=7.6$ Hz, 1H), 7.40 (t, $J=7.6$ Hz, 1H), 7.33 (d, $J=7.4$ Hz, 1H), 7.17 (d, $J=8.2$ Hz, 2H), 6.64 (d, $J=8.8$ Hz, 2H), 2.88 (s, 3H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 252$.

Compound 9d: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]-2-propanol

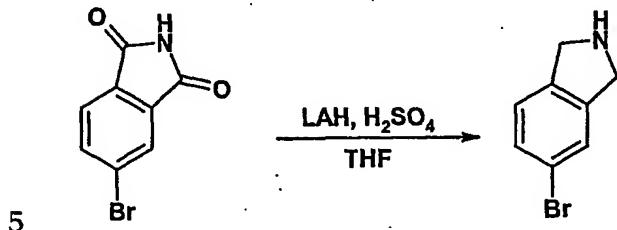


Following General Procedure 5, N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (0.100 g, 0.40 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.085 g, 0.33 mmol) were combined and heated at 70 °C for 24 h. The crude product was 15 purified by reverse phase HPLC (gradient 40-80% CH_3CN in H_2O) to provide the title compound (0.077 g, 42%) as its TFA salt. This material was lyophilized from $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to produce a yellow solid. $^1\text{H-NMR}$ (CD_3OD): δ 8.07-8.02 (m, 2H), 7.71 (d, $J=7.6$ Hz, 1H), 7.57 (t, $J=7.4$ Hz, 1H), 7.46 (t, $J=7.6$ Hz, 1H), 7.29-7.49 (m, 4H), 7.03 (br d, $J=7.6$ Hz, 2H), 4.24-4.14 (m, 3H), 3.79 (dd, $J=5.0$ Hz, $J=14.2$ Hz, 1H), 3.57 (dd, $J=7.2$ Hz, $J=14.4$ Hz, 1H), 3.14 (s, 3H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 465$. Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{F}_4\text{N}_2\text{O}_4 + 0.2 \text{H}_2\text{O} + 0.3 \text{TFA}$: C, 56.44; H, 4.15; N, 5.58. Found: C, 56.41; H, 4.05; N, 5.53.

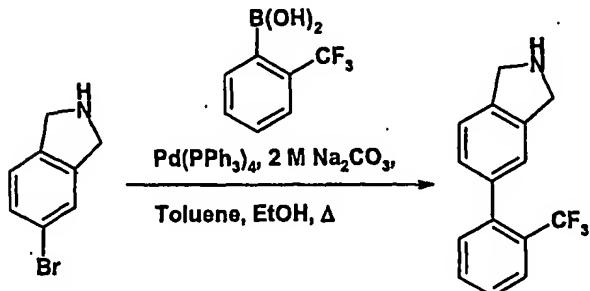
Example 10: α -[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol



Compound 10a: 5-Bromo-2,3-dihydro-1*H*-isoindole

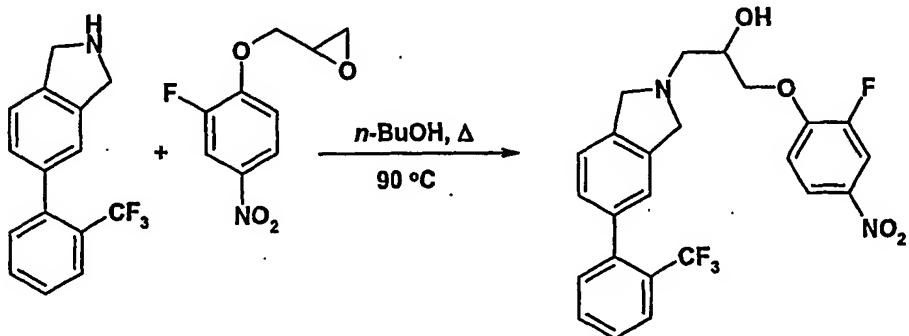


5 A solution of LiAlH₄ (8.8 mL of 1 M solution in Et₂O, 8.8 mmol) in dry THF (13 mL) was cooled to 0 °C. Concentrated H₂SO₄ (0.42 g, 4.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. 5-Bromo-1*H*-isoindole-1,3(2*H*)-dione (0.409 g, 1.81 mmol) was added in portions over 15 minutes, and the reaction 10 was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 2.5h, and then cooled back to 0 °C and quenched by the addition of MeOH (2 mL). Et₂O was added (50 mL), followed by Na₂SO₄·10H₂O. The mixture was stirred vigorously until the organic layer was clear. The mixture was then filtered and concentrated *in vacuo*. Purification by column 15 chromatography (4:1 CH₂Cl₂:MeOH + 0.1% conc. NH₃) provided the title compound (0.128 g, 36%). ¹H-NMR (CDCl₃): δ 7.38 (s 1H), 7.33 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 4.21 (s, 2H), 4.17 (s, 2H), 2.09 (s, 1H). MS (ESI) (M+H)⁺ = 198/200.

Compound 10b: 2,3-Dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole

Following General Procedure 1, 5-bromo-2,3-dihydro-1*H*-isoindole (0.128 g, 0.647 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.184 g, 0.971 mmol) to provide the title compound (0.124 g, 73%) following purification by column chromatography (85:15 CH₂Cl₂:MeOH + 0.1% conc. NH₃). ¹H-NMR (CDCl₃): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=8.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 4.30 (s, 2H), 4.29 (s, 2H), 2.34 (br s, 1H). MS (ESI) (M+H)⁺ = 264.

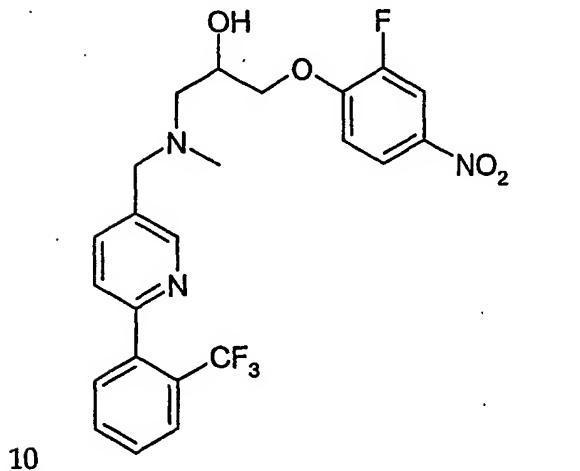
10

Compound 10c: *α*-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol

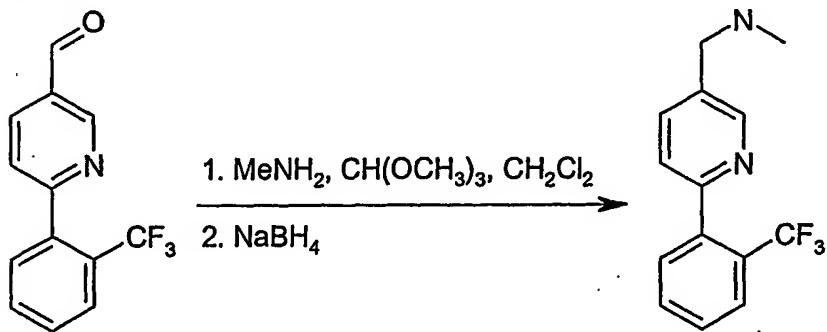
Following General Procedure 5, 2,3-dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole (0.0585 g, 0.222 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0474 g, 0.222 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-65% CH₃CN in H₂O) to provide the title compound (0.0374 g, 29%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile to produce a white, hygroscopic solid. Due to 15 quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts 20 was obtained. ¹H-NMR (CD₃OD): δ 8.13 (ddd, *J*=1.6 Hz, *J*=2.8 Hz, *J*=9.2 Hz, 1H),

8.09 (dd, $J=2.8$ Hz, $J=11.2$ Hz, 1H), 7.81 (d, $J=7.6$ Hz, 1H), 7.68 (t, $J=7.2$ Hz, 1H), 7.59 (t, $J=7.6$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.42-7.33 (m, 4H), 5.08-4.74 (br s, 4H), 4.52 (sextet, $J=4.8$ Hz, 1H), 4.30 (d, $J=4.8$ Hz, 2H), 3.79-3.68 (m, 2H). MS (ESI) $(M+H)^+ = 477$. Anal. Calcd for $C_{24}H_{20}F_4N_2O_4+0.6$ TFA+2.5 H₂O: C, 51.31; H, 4.37; N, 4.75. Found: C, 51.29; H, 4.38; N, 4.54.

Example 11: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]3-pyridinyl]methyl]amino]-2-propanol



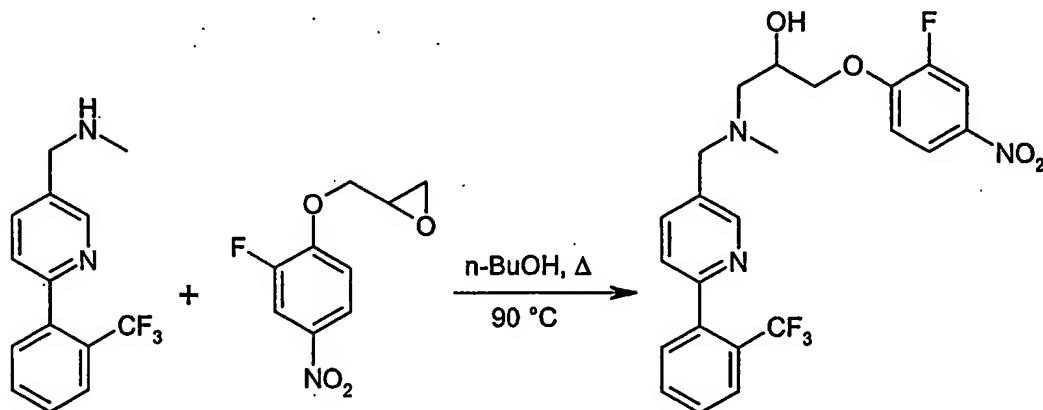
Compound 11a: N-Methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine



15 6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde (0.360 g, 1.43 mmol) was treated according to General Procedure 3 to provide the title compound (0.312 g, 91%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ¹H-NMR (CDCl₃): δ 8.62 (d, $J=1.6$ Hz, 1H), 7.76 (d, $J=7.6$ Hz, 1H), 7.73 (d,

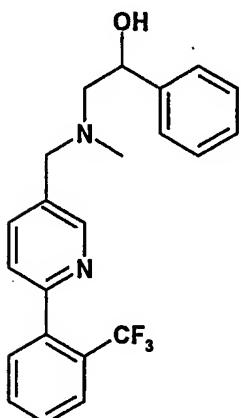
J=2.0 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.54-7.48 (m, 2H), 7.40 (d, *J*=8.0 Hz, 1H), 3.84 (s, 2H), 2.50 (s, 3H). MS (ESI) (M+H)⁺ = 267.

5 **Compound 11b: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]3-pyridinyl]methyl]amino]-2-propanol**



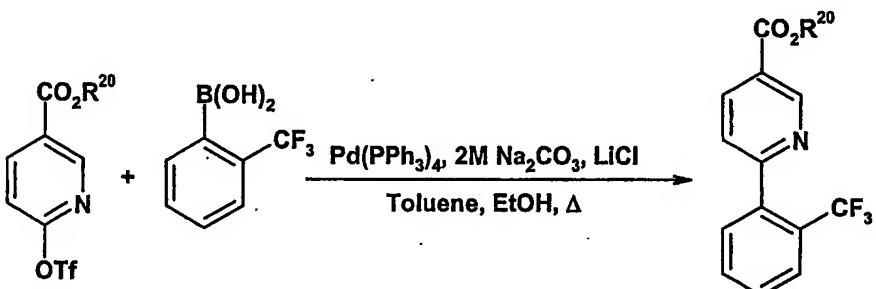
Following General Procedure 5, *N*-methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine (0.100 g, 0.38 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.094 g, 0.38 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-50% CH₃CN in H₂O) to provide the title compound (0.071 g, 31%) as its TFA salt. This material was lyophilized from H₂O/CH₃CN to produce a white solid. ¹H-NMR (CD₃OD): δ 8.78 (d, *J*=1.6 Hz, 1H), 8.13-8.03 (m, 3H), 7.84 (d, *J*=7.6 Hz, 1H), 7.74 (t, *J*=7.2 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.6 Hz, 1H), 4.66 (br s, 1H), 4.53 (br s, 2H), 4.23 (d, *J*=4.8 Hz, 2H), 3.43 (t, *J*=10.0 Hz, 2H), 2.99 (s, 3H). MS (ESI) (M+H)⁺ = 480. Anal. Calcd for C₂₃H₂₁F₄N₃O₄ + 0.8 H₂O + 1.2 TFA: C, 48.37; H, 3.80; N, 6.66. Found: C, 48.37; H, 3.70; N, 6.79.

Example 12: α -[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol



5

Compound 12a: Methyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate and Ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate

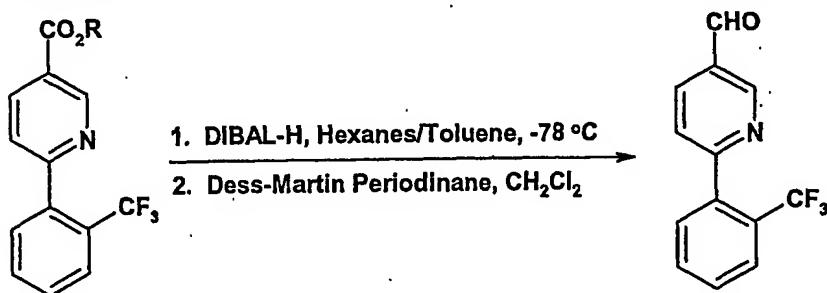


R^{20} = Methyl, or Ethyl

A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.27 g, 12.0 mmol) in ethanol 10 (30 mL) was added to a mixture of methyl 6-[[trifluoromethyl]sulfonyloxy]-3-pyridinecarboxylate (2.27 g, 7.96 mmol), LiCl (1.01 g, 23.9 mmol), $Pd(PPh_3)_4$ (0.46 g, 0.40 mmol), toluene (120 mL), and 2 M Na_2CO_3 (12 mL). The resulting mixture was heated at reflux for 18 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with 15 EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound as a 1:1.4 mixture of the methyl and ethyl esters (1.59 g, 69%). Methyl

ester: $^1\text{H-NMR}$ (CDCl_3): δ 9.30 (dd, $J=0.8$ Hz, $J=2.0$ Hz, 1H), 8.37 (dd, $J=2.4$ Hz, $J=7.2$ Hz, 1H), 7.80 (dd, $J=0.8$ Hz, $J=8.0$ Hz, 1H), 7.65 (t, $J=7.6$ Hz, 1H), 7.67-7.50 (m, 3H), 4.00 (s, 3H). MS (ESI) ($M+\text{H}$) $^+ = 282$. Ethyl ester: $^1\text{H-NMR}$ (CDCl_3): δ 9.29 (dd, $J=0.8$ Hz, $J=2.4$ Hz, 1H), 8.37 (dd, $J=2.4$ Hz, $J=8.4$ Hz, 1H), 7.79 (dd, $J=0.8$ Hz, $J=8.4$ Hz, 1H), 7.65 (t, $J=7.6$ Hz, 1H), 7.60-7.50 (m, 3H), 4.45 (q, $J=7.2$ Hz, 2H), 1.44 (t, $J=7.2$ Hz, 3H). MS (ESI) ($M+\text{H}$) $^+ = 296$.

Compound 12b: 6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde

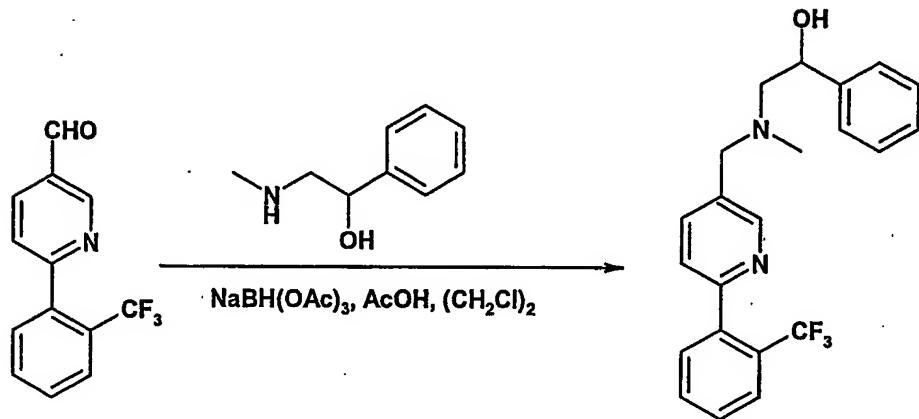


10 DIBAL-H (12.1 mL of a 1 M solution in hexanes, 12.1 mmol) was added dropwise to a solution of a mixture of methyl and ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate (1.59 g of a 1:1.4 mixture, 5.50 mmol) in dry toluene (45 mL) maintained at -78 °C. After the addition was complete, the reaction was stirred at -78 °C for 30 min, and then 12 mL of 1 N HCl was added cautiously and the mixture was 15 allowed to warm to room temperature. Additional water (30 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and Dess-Martin periodinane (2.36 g, 5.57 mmol) was added in portions. After the addition was complete, the 20 reaction was stirred at room temperature for 2 h. The reaction was then quenched with 1:1 saturated NaHCO_3 :saturated $\text{Na}_2\text{S}_2\text{O}_3$ (40 mL) and stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (3:2 Hexanes:EtOAc) 25 to provide the title compound (1.23 g, 89% for the two steps) as a slightly yellow oil which solidified upon storage in the freezer. $^1\text{H-NMR}$ (CDCl_3): δ 10.19 (s, 1H), 9.16

(dd, $J=0.8$ Hz, $J=2.0$ Hz, 1H), 8.25 (dd, $J=2.4$ Hz, $J=8.0$ Hz, 1H), 7.81 (d, $J=8.0$ Hz, 1H), 7.70-7.56 (m, 3H), 7.52 (d, $J=7.6$ Hz, 1H). MS (ESI) ($M+H$)⁺ = 252.

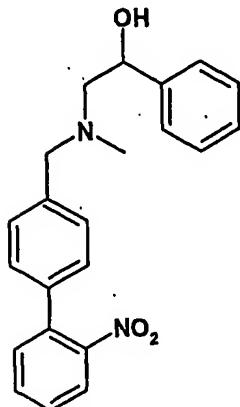
Compound 12c: α -[[Methyl-[[6-[2-(trifluoromethyl)phenyl]phenyl]-3-

5 pyridinyl]methyl]amino]methyl]-benzenemethanol



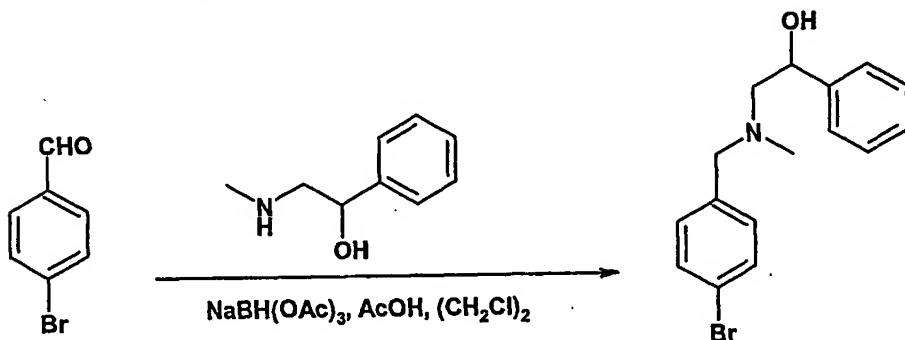
Following General Procedure 4, 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde (0.166 g, 0.66 mmol), α -[(methylamino)methyl]benzenemethanol (0.100 g, 0.66 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.280 g, 1.32 mmol) were combined. The 10 crude product was purified by reverse phase HPLC (gradient 20-40% CH_3CN in H_2O) to provide the title compound (0.279 g, 84%) as its TFA salt. This material was lyophilized from H_2O /acetonitrile to produce a white, hygroscopic solid. $^1\text{H-NMR}$ (CD_3OD): δ 8.81 (s, 1H), 8.14 (d, $J=8.0$ Hz, 1H), 7.86 (d, $J=8.0$ Hz, 1H), 7.57 (t, $J=7.2$ Hz, 1H), 7.72-7.64 (m, 2H), 7.55 (d, $J=7.2$ Hz, 1H), 7.48-7.31 (m, 5H), 5.17 (br m, 1H), 4.54 (br s, 2H), 3.33 (br s, 2H), 3.03 (br s, 3H). MS (ESI) ($M+H$)⁺ = 387. Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_2\text{O}+1.2$ TFA+1.1 H_2O : C, 53.97; H, 4.53; N, 5.16. Found: C, 54.00; H, 4.43; N, 5.52.

Example 13: α -[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol



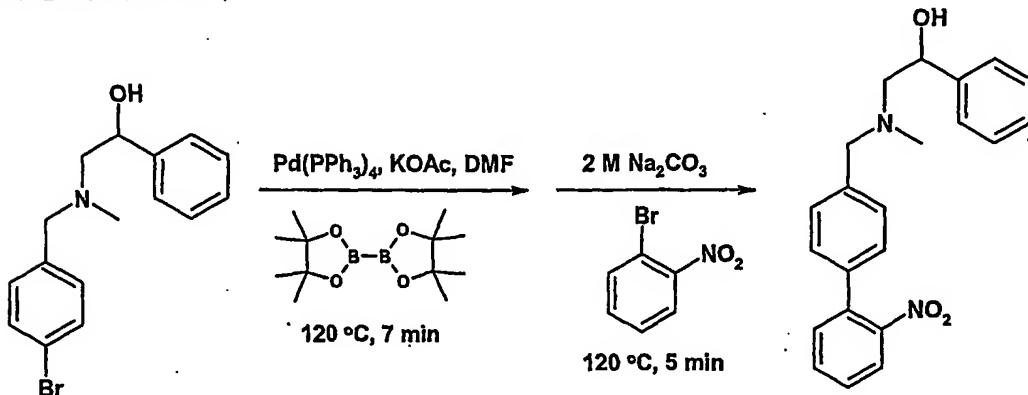
5

Compound 13a: α -[[[(4-Bromophenyl)methyl]methylamino]methyl]benzenemethanol



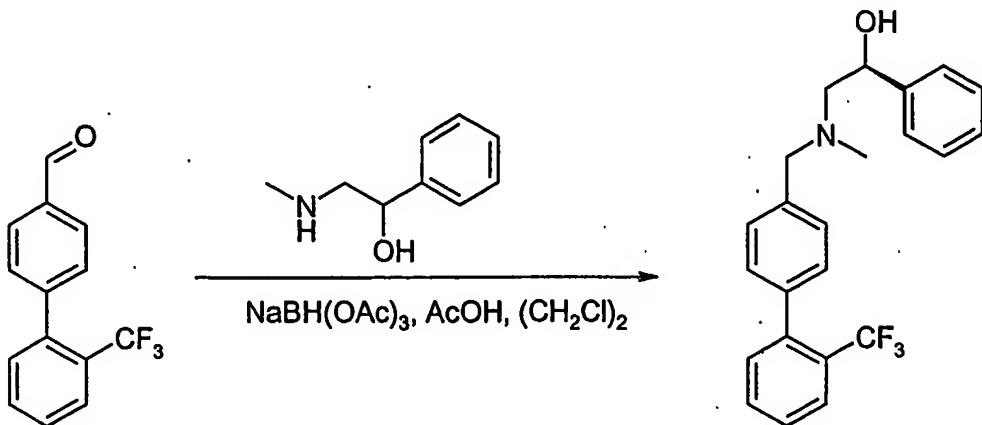
Following General Procedure 4, 4-bromobenzaldehyde (1.22 g, 6.59 mmol), α -10 [(methylamino)methyl]benzenemethanol (0.500 g, 3.31 mmol), and NaBH(OAc)₃ (1.40 g, 6.61 mmol) were combined. The crude product was purified by flash chromatography (Gradient of 100% CH₂Cl₂ to 9:1 CH₂Cl₂:MeOH + 0.1% conc. NH₃) to provide the title compound (0.942 g, 89%). ¹H-NMR (CD₃OD): δ 7.48-7.44 (m, 2H), 7.36-7.32 (m, 4H), 7.32-7.24 (m, 1H), 7.21-7.17 (m, 2H), 4.75 (dd, *J*=3.6 Hz, 15 *J*=10.4 Hz, 1H), 3.69 (d, *J*=13.2 Hz, 1H), 3.48 (d, *J*=13.2 Hz, 1H), 2.59 (half of d of AB_q, *J*=10.4 Hz, *J*=12.4 Hz, 1H), 2.52 (half of d of AB_q, *J*=3.2 Hz, *J*=12.4 Hz, 1H), 2.31 (s, 3H). MS (ESI) (M+H)⁺ = 320/322.

Compound 13b: α -[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol



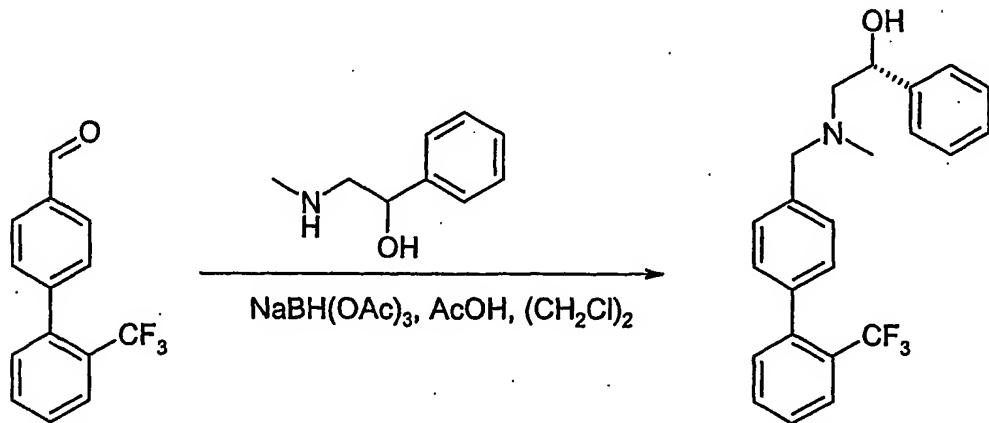
5 Following General Procedure 2, α -[[[(4-bromophenyl)methyl]amino]methyl]benzenemethanol (0.0530 g, 0.165 mmol) and bis(pinacolato)diboron (0.0462 g, 0.182 mmol) were combined. The resulting boronate ester was used for the reaction with 1-bromo-2-nitrobenzene (0.0669 g, 0.331 mmol) as the second aryl halide. The crude product was purified by reverse phase HPLC (gradient 25-45% CH_3CN in H_2O) to provide the title compound (0.0113 g, 14%) as its TFA salt. This material was lyophilized from H_2O /acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $^1\text{H-NMR}$ (CD_3OD): δ 7.96 (d, $J=8.0$ Hz, 1H), 7.75 (t, $J=7.2$ Hz, 1H), 7.70-7.57 (br m, 3H), 7.57-7.29 (br m, 8H), 5.11 (dd, $J=3.6$ Hz, $J=10.8$ Hz, 1H), 4.75 (br d, $J=12.8$ Hz, 0.5H), 4.54-4.44 (br m, 1H), 4.32 (br d, $J=12.0$ Hz, 0.5H), 3.48-3.15 (br m, 2H), 3.07 (s, 1.5H), 2.91 (s, 1.5H). $\text{MS (ESI)} (\text{M}+\text{H})^+ = 363$. Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_3 + 1.1 \text{ TFA} + 1.1 \text{ H}_2\text{O}$: C, 57.25; H, 5.02; N, 5.52. Found: C, 57.26; H, 4.97; N, 5.46.

Example 14: (α^1S)- α -[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol



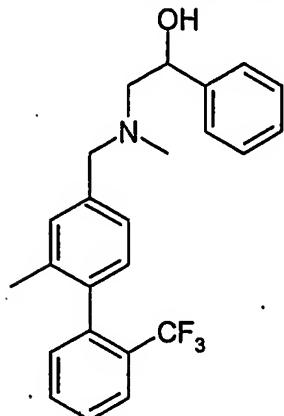
Following General Procedure 4, 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α -[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL[®]OD (990:10:1 EtOH:Hex:Et₂NH) gave the title compound. The HCl salt of the title compound (0.0102 g, 3%) was prepared using 1M HCl in Et₂O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{24} = +44.2^\circ$ (c=1.02, MeOH). ¹H-NMR (CD₃OD): δ 7.80 (d, $J=7.6$ Hz, 1H), 7.69-7.56 (overlapping t at 7.67 and m, $J=7.4$ Hz, 4H), 7.46-7.32 (overlapping d at 7.45 and br m, $J=8.0$ Hz, 8H), 5.11 (dd, $J=6.8$ Hz, $J=7.2$ Hz, 1H), 4.85-4.35 (br m, 2H), 3.26 (br s, 2H), 3.00 (br s, 3H). MS (ESI) (M+H)⁺ = 386. Anal. Calcd for C₂₃H₂₂F₃NO + 0.1 H₂O + 1.2 HCl: C, 64.10; H, 5.47; N, 3.25. Found: C, 64.15; H, 5.33; N, 3.80.

Example 15: (α^1R)- α -{[Methyl|[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

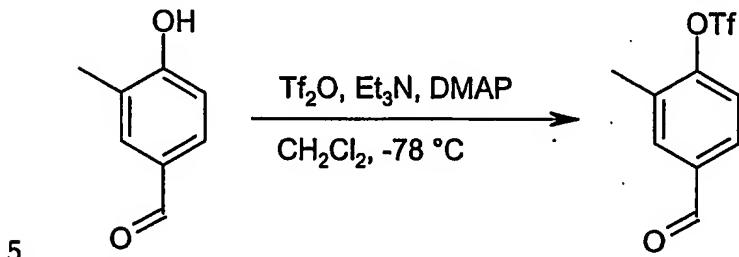


Following General Procedure 4, 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α -[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL[®]OD (990:10:1 EtOH:Hex:Et₂NH) gave the title compound. The HCl salt of the title compound (0.0056 g, 2%) was prepared using 1M HCl in Et₂O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{28} = -49.5^\circ$ (c=0.56, MeOH). ¹H-NMR (CD₃OD): δ 7.79 (d, $J=8.0$ Hz, 1H), 7.68-7.55 (overlapping t at 7.66 and m, $J=7.6$ Hz, 4H), 7.45-7.30 (overlapping d at 7.44 and br m, $J=7.6$ Hz, 8H), 5.10 (dd, $J=6.4$ Hz, $J=7.6$ Hz, 1H), 4.84-4.33 (br m, 2H), 3.25 (br s, 2H), 2.98 (br s, 3H). MS (ESI) (M+H)⁺ = 386. Anal. Calcd for C₂₃H₂₂F₃NO + 1.5 HCl: C, 62.77; H, 5.38; N, 3.18. Found: C, 62.89; H, 5.31; N, 3.40.

Example 16: α -[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol



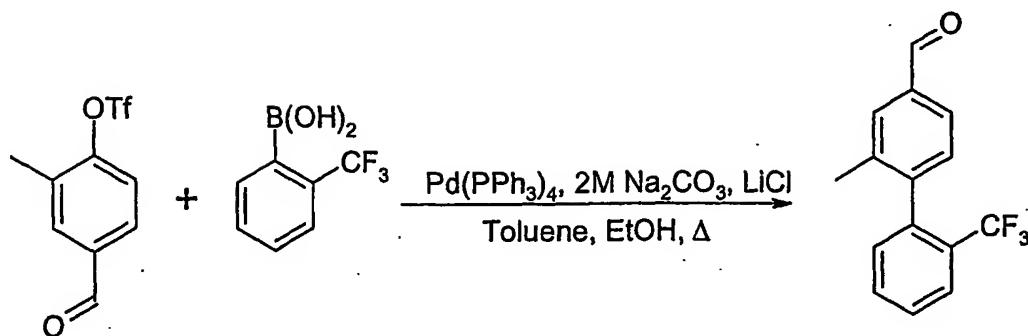
Compound 16a: 4-Formyl-2-methylphenyl trifluoromethanesulfonate



Following General Procedure 7, 4-hydroxy-3-methylbenzaldehyde (0.500 g, 3.67 mmol), DMAP (0.045 g, 0.37 mmol), NEt₃ (1.126 mL, 8.08 mmol), and triflic anhydride (1.139 g, 4.04 mmol) were combined. Silica gel column chromatography (8:2 Hexanes:EtOAc) provided the title compound (0.896 g, 91%) as a white solid.

10 ¹H-NMR (CDCl₃): δ 10.01 (s, 1H), 7.86 (s, 1H), 7.81 (d, J =8.0 Hz, 1H), 7.44 (d, J =7.6 Hz, 1H), 2.48 (s, 3H).

Compound 16b: 2-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde

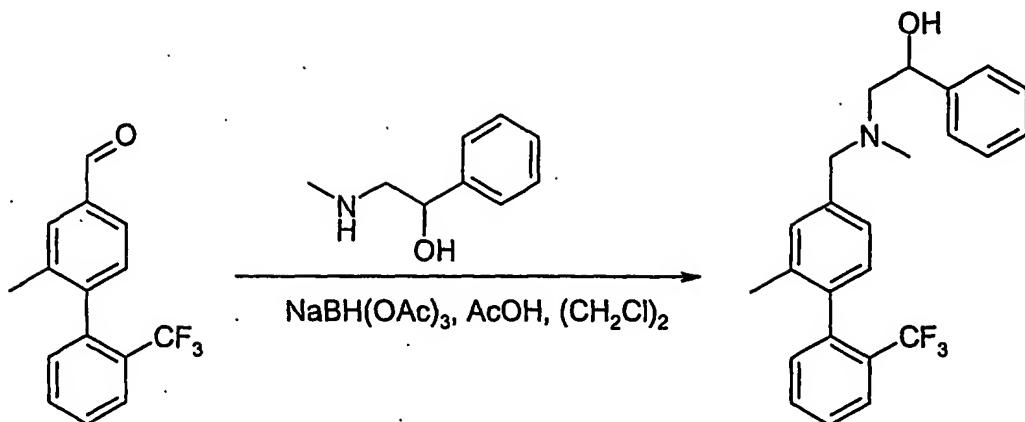


A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.79 g, 14.66 mmol) in ethanol (35 mL) was added to a mixture of 4-formyl-2-methylphenyl

5 trifluoromethanesulfonate (2.62 g, 9.78 mmol), LiCl (1.24 g, 29.33 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.57 g, 0.49 mmol), toluene (145 mL), and 2 M Na_2CO_3 (15 mL). The resulting mixture was heated at reflux for 24 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the title compound (2.533 g, 95%). The crude material was of sufficient purity (>85%) to be used in subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 10.04 (s, 1H), 7.80-7.78 (overlapping s at 7.78 and d at 7.79, $J=7.6$ Hz, 2H), 7.73 (d, $J=7.6$ Hz, 1H), 7.61 (t, $J=7.6$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 1H), 7.32 (d, $J=8.0$ Hz, 1H), 7.22 (d, $J=7.6$ Hz, 1H), 2.12 (s, 3H).

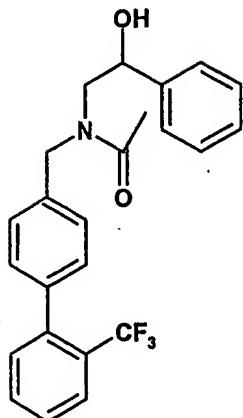
10 15 MS (ESI) ($\text{M}+\text{H}$)⁺ = 265.

Compound 16c: α -[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

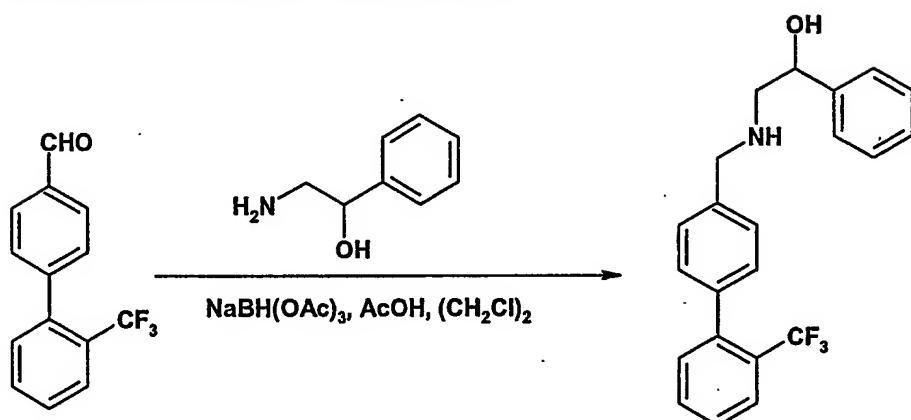


Following General Procedure 4, 2-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (1.076 g, 3.55 mmol), α -[(methylamino)methyl]benzenemethanol (0.200 g, 1.32 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.562 g, 2.65 mmol) were combined. The crude product was purified by reverse phase HPLC (gradient 30-85% CH_3CN in H_2O) to provide the title compound (0.267 g, 40%) as its TFA salt. This material was lyophilized from H_2O /acetonitrile to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^1H -NMR (CD_3OD): δ 7.80 (d, $J=7.6$ Hz, 1H), 7.66 (t, $J=7.6$ Hz, 1H), 7.57 (t, $J=7.6$ Hz, 1H), 7.47-7.22 (overlapping d at 7.26 and br m, $J=7.6$ Hz, 9H), 5.09 (dd, $J=3.2$ Hz, $J=10.8$ Hz, 1H), 4.69 (br d, $J=12.4$ Hz, 0.5H), 4.47-4.37 (br m, 1H), 4.25 (br d, $J=13.2$ Hz, 0.5H), 3.41-3.13 (br m, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H), 2.07-2.05 (overlapping s at 2.07 and s at 2.05, 3H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 400$. Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{F}_3\text{NO} + 0.1 \text{ H}_2\text{O} + 1.1 \text{ TFA}$: C, 59.75; H, 4.84; N, 2.66. Found: C, 59.73; H, 4.81; N, 2.75.

Example 17: *N*-(2-Hydroxy-2-phenylethyl)-*N*-[(2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]acetamide



Compound 17a: α -[[[2'-(Trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

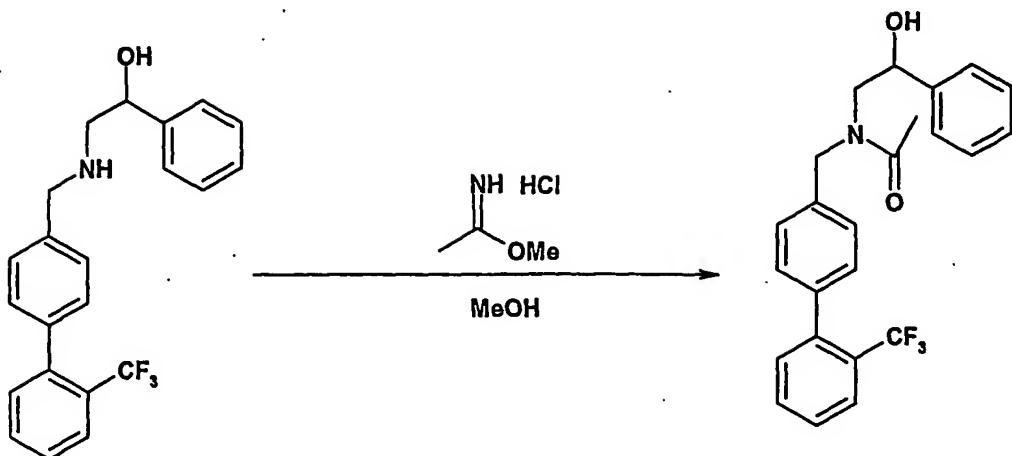


5

Following General Procedure 4, 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (0.121 g, 0.484 mmol), α -(aminomethyl)benzenemethanol (0.0975 g, 0.711 mmol), and $\text{NaBH}(\text{OAc})_3$ (0.179 g, 0.846 mmol) were combined. The crude product was purified by flash chromatography (9:1 CH_2Cl_2 :MeOH) to provide the title compound (0.133 g, 74%). $^1\text{H-NMR}$ (CDCl_3): δ 7.74 (d, $J=8.0$ Hz, 1H), 7.55 (t, $J=7.2$ Hz, 1H), 7.46 (t, $J=8.0$ Hz, 1H), 7.40-7.27 (m, 10H), 4.78 (dd, $J=3.6$ Hz, $J=8.8$ Hz, 1H), 3.89 (AB_q, $J=13.2$ Hz, 2H), 2.98 (dd, $J=3.6$ Hz, $J=12.0$ Hz, 1H), 2.81 (overlapping dd and br s, $J=9.2$ Hz, $J=12.4$ Hz for dd, 3H). MS (ESI) ($\text{M}+\text{H}$)⁺ = 372.

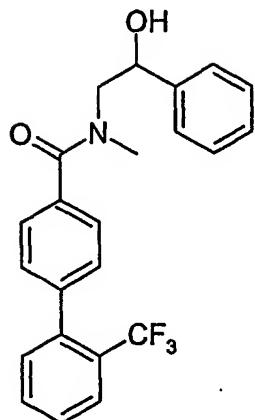
10

15 **Compound 17b: *N*-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide**

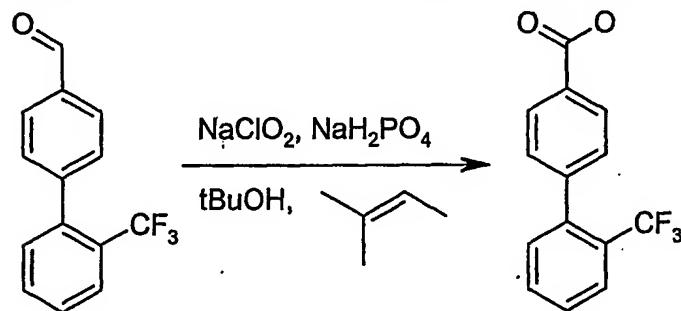


Methyl acetimidate hydrochloride (0.0847 g, 0.773 mmol) was added to a solution of α -[[[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol (0.0287 g, 0.0773 mmol) in dry MeOH (1 mL) maintained at 0 °C. The reaction was stirred for 6 d at room temperature, and then an additional portion of methyl acetimidate hydrochloride (0.0500 g, 0.456 mmol) was added. After stirring an additional 7 d, the reaction was concentrated *in vacuo*. The residue was dissolved in EtOAc (2 mL) and washed with a saturated solution of Na₂CO₃ (1 mL). The aqueous phase was back-extracted with additional EtOAc (3 x 1 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to provide the title compound (0.0105 g, 33%). This material was lyophilized from H₂O/acetonitrile. Due to hindered rotation about the amide bond, rotamers were observed in the ¹H-NMR spectrum. ¹H-NMR (CD₃OD): δ 7.78-7.74 (m, 1H), 7.66-7.60 (m, 1H), 7.56-7.50 (m, 1H), 7.40-7.20 (m, 10H), 5.00 (dd, J =4.8 Hz, J =8.4 Hz, 0.4H), 4.93 (dd, J =4.8 Hz, J =8.0 Hz, 0.6H), 4.88 (d, J =14.8 Hz, 0.6H), 4.72 (d, J =17.2 Hz, 0.4H), 4.61-4.54 (m, 1H), 3.67-3.58 (m, 1H), 3.50 (dd, J =8.4 Hz, J =13.6 Hz, 0.4H), 3.39 (dd, J =4.8 Hz, J =15.2 Hz, 0.6H), 2.16 (s, 1.2H), 2.11 (s, 1.8H). MS (ESI) (M+H)⁺ = 414. Anal. Calcd for C₂₄H₂₂F₃NO₂+0.3 TFA+0.6 H₂O: C, 64.45; H, 5.17; N, 3.06. Found: C, 64.55; H, 5.10; N, 3.50.

Example 18: N-(2-Hydroxy-2-phenylethyl)-N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide

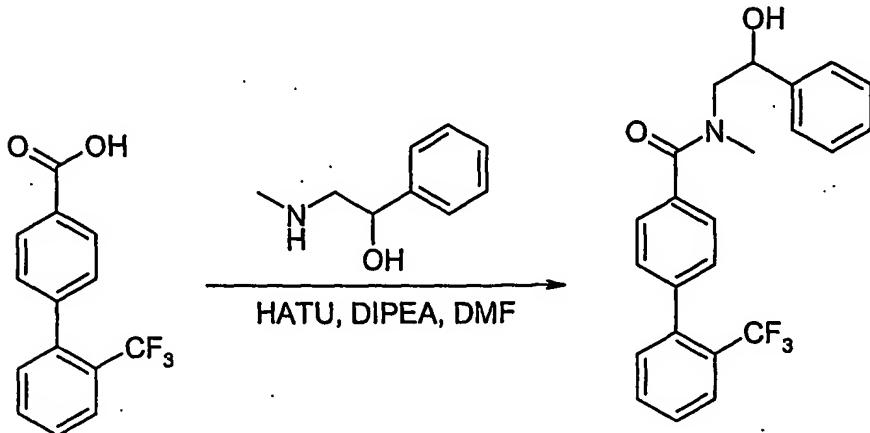


Compound 18a: 2'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid



To a solution of 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.147 g, 0.59 mol) in t-BuOH (9 mL) and 2-methyl-2-butene (9 mL) was added a solution of NaClO₂ (0.496, 5.50 mmol) and NaH₂PO₄ (0.588 g, 4.9 mmol) in water (6 mL) in four portions over 0.5 h. The resulting reaction mixture was stirred for 5 h at room temperature, concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with CH₂Cl₂ (3 x). The product in the combined organic phases was then extracted into 1 N NaOH (3 x). The CH₂Cl₂ layer was discarded, the combined aqueous layers were acidified with 1 N HCl, and the product was back extracted with CH₂Cl₂ (3 x). The combined organic phases were then dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide the title compound (0.125 g, 80%) as a white solid. The crude material was of sufficient purity (>90%) to be used in subsequent steps. ¹H-NMR (CD₃OD): δ 8.06 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.42-7.36 (overlapping d at 7.41 and d at 7.37, *J*=8.0 Hz for both d, 3H).

Compound 18b: *N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide



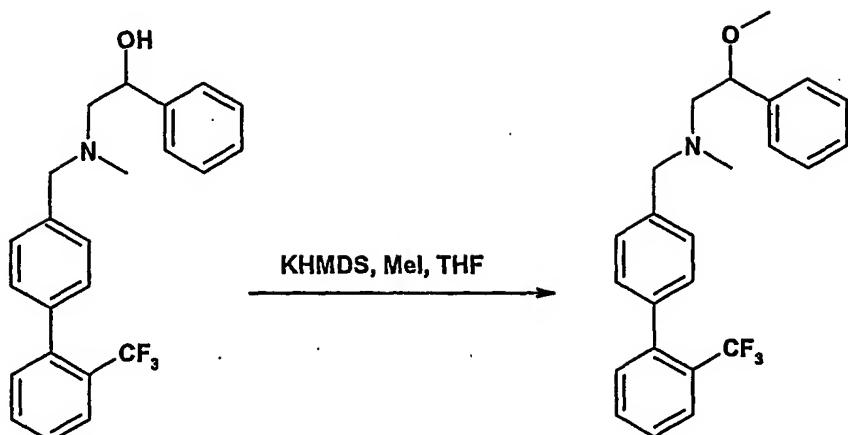
A solution of α -[(methylamino)methyl]benzenemethanol (0.013 g, 0.085 mmol) in

5 DMF (0.5 mL) was added to a solution of 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid (0.025 g, 0.094 mmol), HATU (0.036 g, 0.094 mmol) and DIPEA (0.022 mL, 0.128 mmol) in DMF (0.5 mL). The reaction was carried out in a 48-well plate. The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in EtOAc (1 mL), and washed with 1 N NaOH (3 x 1 mL) and water (2 x

10 1 mL). The organic phase was concentrated *in vacuo* to provide the title compound (0.027 g, 81%) with >90% purity. Due to hindered rotation about the amide bond, rotamers were observed in the ^1H -NMR spectrum. ^1H -NMR (CD_3OD): δ 7.77 (dd, $J=2.0$ Hz, $J=7.6$ Hz, 1H), 7.64 (t, $J=7.4$ Hz, 1H), 7.54 (t, $J=7.6$ Hz, 1H), 7.46 (d, $J=7.6$ Hz, 1H), 7.40-7.22 (d at 7.30, $J=8.0$ Hz, d at 7.23, $J=8.0$ Hz, br m, 8H), 7.10-

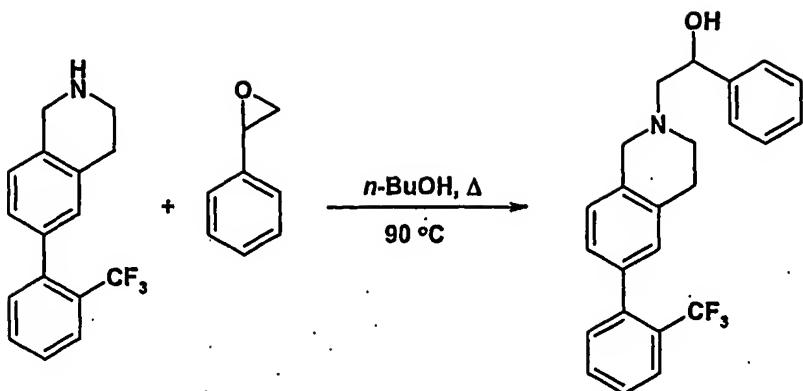
15 7.08 (m, 1H), 5.08 (t, $J=6.6$ Hz, 0.5H), 4.81 (t, $J=6.4$ Hz, 0.5H), 3.74-3.72 (m, 1H), 3.50 (t, $J=6.6$ Hz, 1H), 3.21 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) ($M+\text{H}$) $^+ = 400$.

Example 19: β -Methoxy-*N*-methyl-*N*-[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-benzeneethanamine



KHMDS (0.45 mL of 0.5M in toluene, 0.225 mmol) was added to a solution of α -[[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzene-methanol (0.0286 g, 0.0742 mmol) in dry THF (3 mL). The mixture was stirred at room temperature for 20 min, and then neat iodomethane (4.6 μ L, 0.074 mmol) was added. The reaction was stirred at room temperature for 19 h, and then quenched by the addition of H_2O (3 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic phases were then dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-70% CH_3CN in H_2O) to provide the title compound (0.0066 g, 17%) as its TFA salt. This material was lyophilized from H_2O /acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $^1\text{H-NMR}$ (CD_3OD): δ 7.82 (d, $J=7.6$ Hz, 1H), 7.72-7.56 (m, 4H), 7.54-7.30 (m, 8H), 4.78-4.65 (m, 1H), 4.62-4.42 (m, 1.5H), 4.36 (br d, $J=12.4$ Hz, 0.5H), 3.50-3.30 (m, 1.5H), 3.29 (s, 3H), 3.17 (br d, $J=12.8$ Hz, 0.5H), 3.06 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 400$.

Example 20: 3,4-Dihydro- α -phenyl-6-[2-(trifluoromethyl)phenyl]-2(1H)-isoquinolineethanol

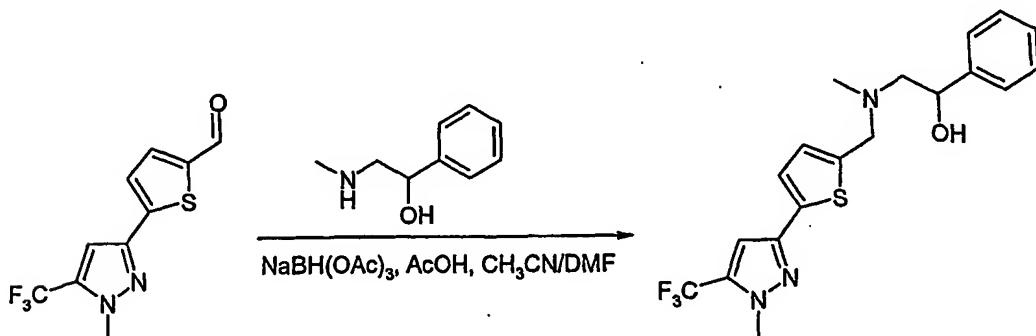


Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0247 g, 0.0891 mmol) and 2-(phenyl)oxirane (0.010 mL, 0.0877 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified

5 by reverse phase HPLC (gradient 25-45% CH₃CN in H₂O) to provide the title compound (0.0111 g, 24%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.79 (d, *J*=7.6 Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.24 (m, 5H), 5.27 (dd, *J*=3.2 Hz, *J*=10.0 Hz, 1H), 4.86-4.46 (br m, 2H), 4.12-3.90 (br m, 1H), 3.62-3.12 (br m, 5H). MS (ESI) (M+H)⁺ = 398. Anal. Calcd for C₂₄H₂₂F₃NO+1.3 TFA+0.5 H₂O: C, 57.60; H, 4.42; N, 2.53. Found: C, 57.60; H, 4.35; N, 2.49.

10

15 Example 21: α -[[Methyl[[5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl]methyl]amino]methyl]-benzenemethanol



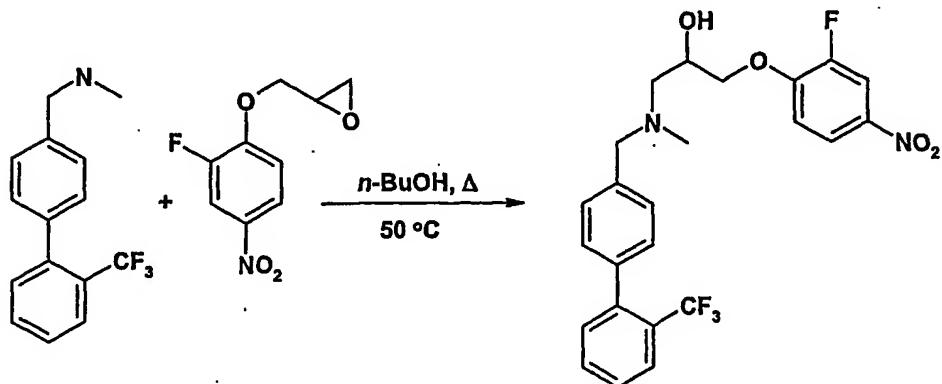
A solution of 5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thiophenecarboxaldehyde (0.260 g, 0.77 mmol), α -

[(methylamino)methyl]benzenemethanol (0.151 g, 0.77 mmol), and acetic acid (0.080 mL) in CH₃CN (4 mL) was stirred for 3 days. A solution of NaBH(OAc)₃ (0.211 g, 3.87 mmol) in DMF (4 mL) was added and the reaction was stirred for 2 days, concentrated *in vacuo*, redissolved in CH₂Cl₂, and washed with 1 N NaOH. The 5 layers were then filtered through a Hydromatrix[®] column and the product was eluted with CH₂Cl₂. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 15-85% CH₃CN in H₂O) to provide the title compound (0.040 g, 10%) as its TFA salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.41-7.28 (br m, 7H), 6.81 (s, 1H), 5.10 (dd, *J*=6.0 Hz, *J*=7.6 Hz, 1H), 4.80-4.65 (br s at 4.75, s at 10 4.69, and s at 4.65, 2H), 4.01 (s, 3H), 3.33-3.27 (overlapping s at 3.33 and s at 3.30, 2H), 3.01 (br s, 3H). MS (ESI) (M+H)⁺ = 396. Anal. Calcd for C₁₉H₂₀F₃N₃OS + 0.2 H₂O + 1.0 TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.

15

20

Example 22: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol

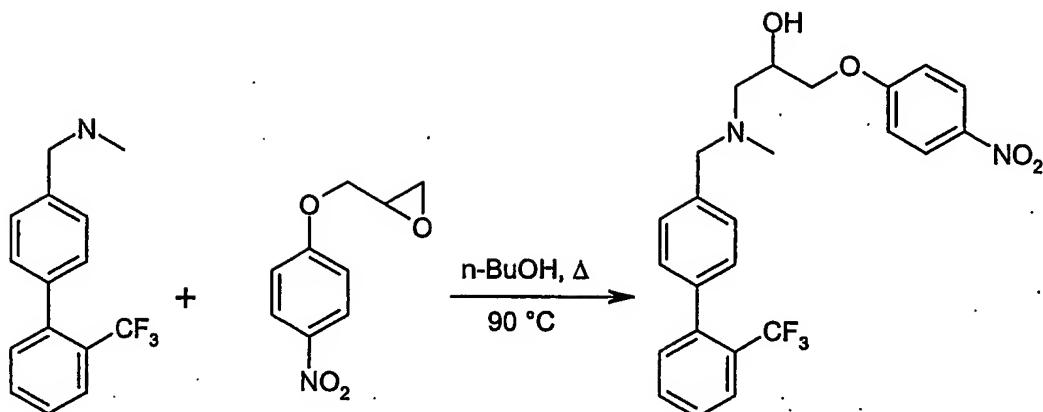


Following General Procedure 5, N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.0800 g of 90% purity, 0.288 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.0613 g, 0.288 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-5 60% CH₃CN in H₂O) to provide the title compound (0.030 g, 18%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 8.08 (d, *J*=9.2 Hz, 1H), 8.04 (dd, *J*=2.0 Hz, *J*=11.2 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 2H), 7.57 (t, *J*=7.6 Hz, 1H), 10 7.44 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.4 Hz, 1H), 4.72-4.16 (br m at 4.51, br s at 4.21, and underlying br m, 5H), 3.62-3.24 (br s at 3.55, br t at 3.40, br s at 3.28, *J*=11.2 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) (M+H)⁺ = 479. Anal. Calcd for C₂₄H₂₂F₄N₂O₄ + 0.1 H₂O + 1.2 TFA: C, 51.39; H, 3.82; N, 4.54. Found: C, 51.34; H, 3.73; N, 4.90.

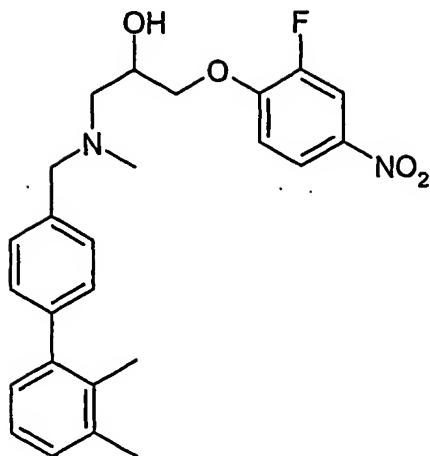
15

20

Example 23: 1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-(4-nitrophenoxy)-2-propanol

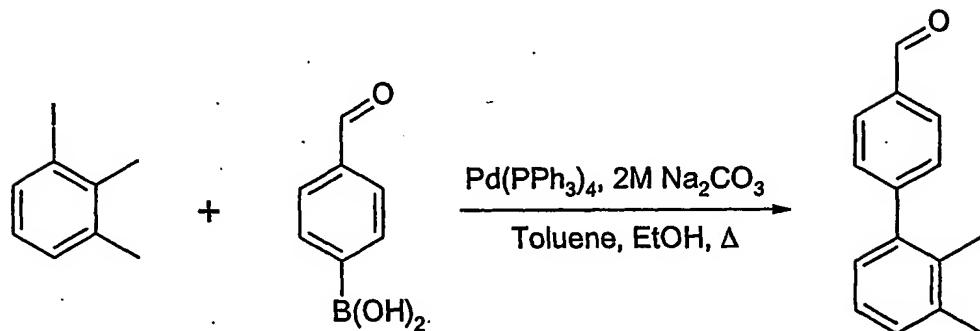


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.29 mmol) and 2-[4-nitrophenoxy]methyl-oxirane (0.057 g, 0.29 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to provide the title compound (0.034 g, 20%) as its TFA salt. This material was lyophilized from H₂O/CH₃CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 8.20 (d, *J*=9.2 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.62-7.55 (overlapping d at 7.61 and t at 7.57, *J*=8.4 Hz for d and *J*=7.6 Hz for t, 3H), 7.44 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=7.6 Hz, 1H), 7.09 (br d, *J*=8.4 Hz, 2H), 4.64-4.31 (overlapping br s at 4.64, br s at 4.31, and br m, 3H), 4.13 (br s, 2H), 3.53-3.29 (br s at 3.53, br t at 3.38, and br s at 3.29, *J*=11.6 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) 15 (M+H)⁺ = 461. Anal. Calcd for C₂₄H₂₃F₃N₂O₄ + 0.2 H₂O + 1.0 TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.



Compound 24a: 2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde

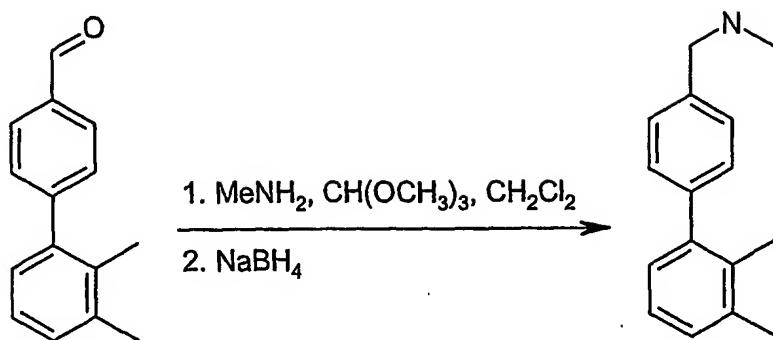
5



Following General Procedure 1, 1-iodo-2,3-dimethylbenzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.05 g, 56%). The crude material was of sufficient purity (>75%) to be used in the subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 10.07 (s, 1H), 7.93 (d, $J=7.6$ Hz, 2H), 7.47 (d, $J=8.0$ Hz, 2H), 7.22-7.15 (m, 2H), 7.07 (d, $J=6.4$ Hz, 1H), 2.36 (s, 3H), 2.15 (s, 3H).

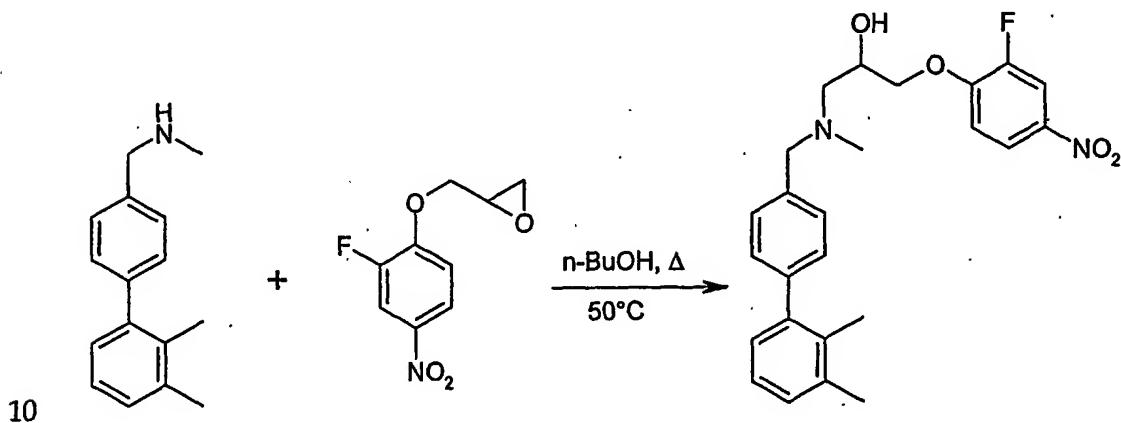
15

Compound 24b: *N*,2',3'-Trimethyl-[1,1'-biphenyl]-4-methanamine



2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.351 g, 1.67 mmol) was treated according to General Procedure 3 to provide the title compound (0.120 g, 40%). The crude material was of sufficient purity (>80%) to be used in subsequent steps. ¹H-NMR (CDCl₃): δ 7.34 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 7.15-7.06 (m, 3H), 3.79 (br s, 2H), 2.49 (br s, 3H), 2.33 (s, 3H), 2.15 (s, 3H). MS (ESI) (M+H)⁺ = 226.

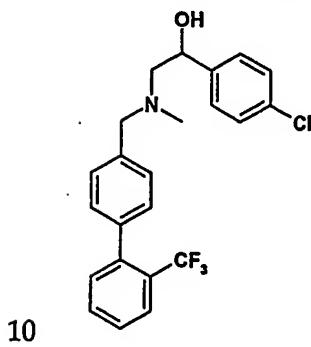
5 10 Compound 24c: 1-[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



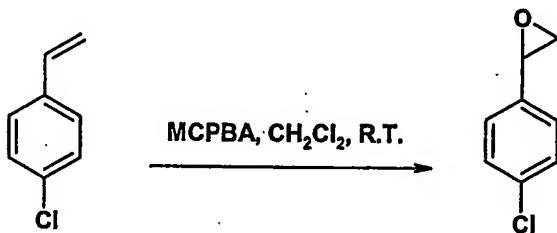
Following General Procedure 5, *N*,2',3'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.063 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified 15 by reverse phase HPLC (gradient 20-60% CH₃CN in H₂O) to provide the title compound (0.027 g, 16%) as its TFA salt. This material was lyophilized from H₂O/CH₃CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 8.09-8.02 (br m, 2H), 7.58 (d, *J*=8.0 Hz, 2H), 7.40 (d, *J*=8.0 Hz, 2H), 7.29 (br s, 1H), 7.15

(d, $J=6.8$ Hz, 1H), 7.10 (t, $J=7.4$ Hz, 1H), 6.98 (d, $J=6.8$ Hz, 1H), 4.62, (br s, 0.5H), 4.49 (br s, 2H), 4.27-4.26 (overlapping br s at 4.27 and br s at 4.26, 2.5H), 3.54-3.28 (br s at 3.54, br s at 3.39, and br s at 3.29, 2H), 3.00-2.95 (overlapping br s at 3.00 and br s at 2.95, 3H), 2.32 (s, 3H), 2.11 (s, 3H). MS (ESI) ($M+H$)⁺ = 439. Anal. Calcd for $C_{25}H_{27}FN_2O_4 + 0.1 H_2O + 1.6 TFA$: C, 54.39; H, 4.66; N, 4.50. Found: C, 54.30; H, 4.48; N, 4.41.

Example 25: 4-Chloro- α -[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

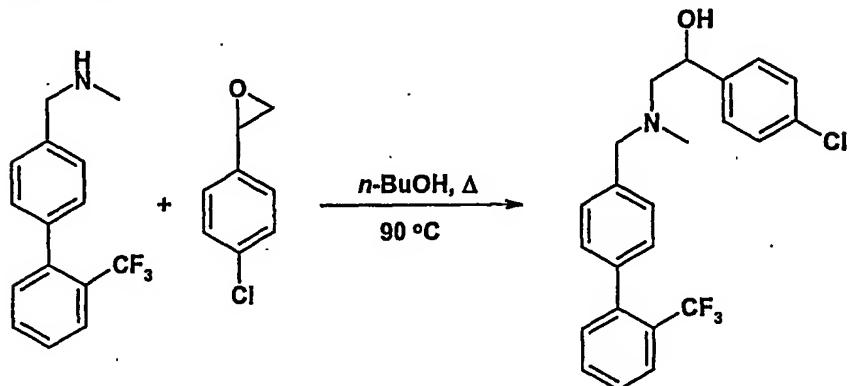


Compound 25a: 2-(4-Chlorophenyl)oxirane



A solution of MCPBA (1.50 g of 60% purity, 5.22 mmol) in CH_2Cl_2 (10 mL) was
15 added to a solution of 1-chloro-4-ethenylbenzene (0.554 g, 4.00 mmol) in CH_2Cl_2 (10 mL) maintained at 0 °C. The reaction was allowed to slowly warm to room temperature and stirred for 24 h. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1
20 Hexanes:EtOAc) to provide the title compound (0.198 g, 32%). ¹H-NMR ($CDCl_3$): δ 7.31 (d, $J=8.8$ Hz, 2H), 7.20 (d, $J=8.8$ Hz, 2H), 3.83 (distorted t, $J=3.6$ Hz, 1H), 3.14 (dd, $J=4.0$ Hz, $J=5.6$ Hz, 1H), 2.75 (dd, $J=2.4$ Hz, $J=5.6$ Hz, 1H).

Compound 25b: 4-Chloro- α -[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol



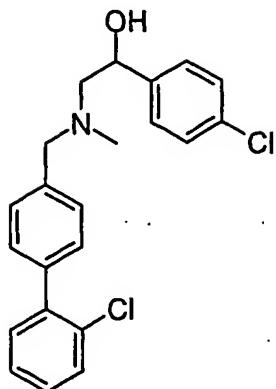
5 Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.114 g of 90% purity, 0.387 mmol) and 2-(4-chlorophenyl)oxirane (0.060 g, 0.387 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH₃CN in H₂O) to provide the title compound (0.051 g, 24%) as its TFA salt. This material was

10 lyophilized from H₂O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.78 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.62-7.52 (t and overlapping br m, *J*=7.6 Hz for t, 3H), 7.48-7.31 (m, 7H), 5.12-5.04 (m, 1H), 4.73 (br d, *J*=13.2 Hz, 0.5H), 4.45 (br m, 1H), 4.27 (br d, *J*=11.6 Hz, 0.5H), 3.46-3.12 (m, 2H), 3.03 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) (M+H)⁺ = 420. Anal. Calcd for C₂₃H₂₁ClF₃NO+1.2 TFA+0.1 H₂O: C, 54.62; H, 4.04; N, 2.51. Found: C, 54.63; H, 3.83; N, 2.52.

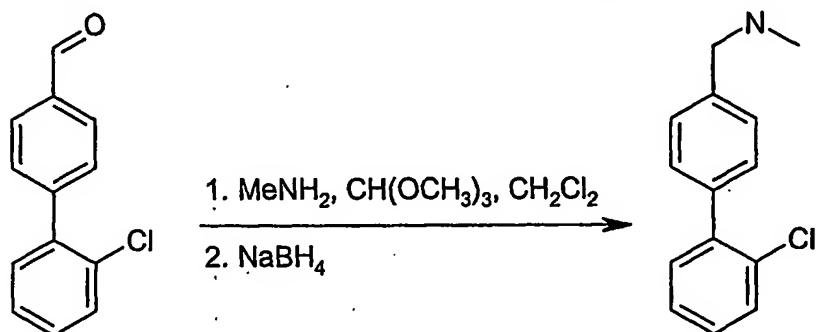
15

Example 26: 4-Chloro- α -[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

25



Compound 26a: 2'-Chloro-N-methyl-[1,1'-biphenyl]-4-methanamine

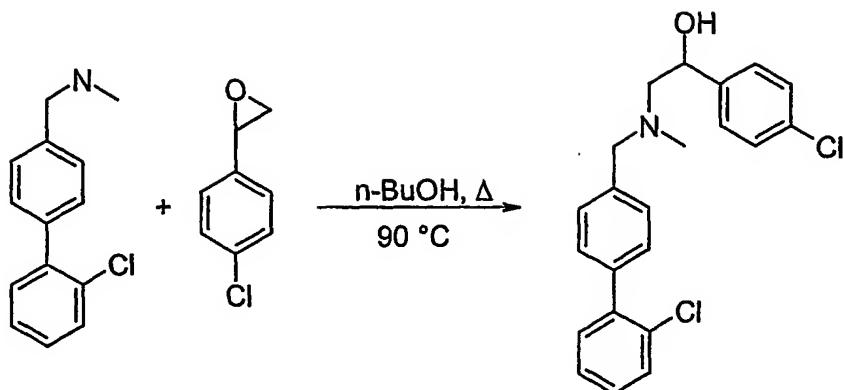


5 2'-Chloro-[1,1'-biphenyl]-4-carboxaldehyde (0.434 g, 2.00 mmol) was treated according to General Procedure 3 to provide the title compound (0.278 g, 75%). The crude material was of sufficient purity (>75%) to be used in subsequent steps. MS (ESI) $(M+H)^+$ = 232.

10

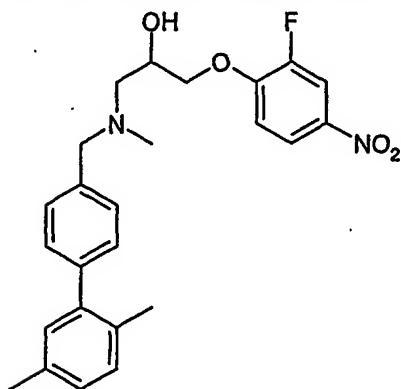
15

Compound 26b: 4-Chloro- α -[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

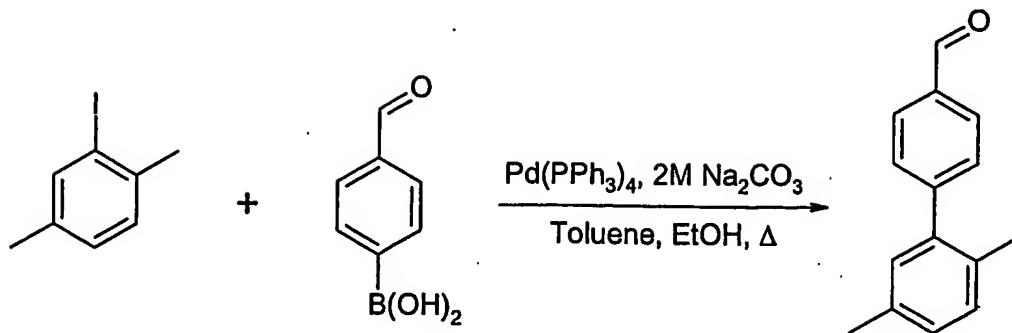


Following General Procedure 5, 2'-chloro-*N*-methyl-[1,1'-biphenyl]-4-methanamine (0.116 g, 0.50 mmol) and 2-(4-chlorophenyl)oxirane (0.078 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH₃CN in H₂O) to provide the title compound (0.074 g, 30%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.63-7.50 (br m, 5H), 7.38 (br s, 7H), 5.11 (dd, *J*=3.4 Hz, *J*=10.6 Hz, 1H), 4.74 (br d, *J*=12.0 Hz, 0.5H), 4.47 (br s, 1H), 4.29 (br d, *J*=12.0 Hz, 0.5H), 3.41-3.17 (br d at 3.42, and br m, *J*=9.6 Hz for d, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) (M+H)⁺ = 386. Anal. Calcd for C₂₂H₂₁Cl₂NO + 0.1 H₂O + 1.1 TFA: C, 56.60; H, 4.38; N, 2.73. Found: C, 56.49; H, 4.28; N, 2.70.

Example 27: 1-[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



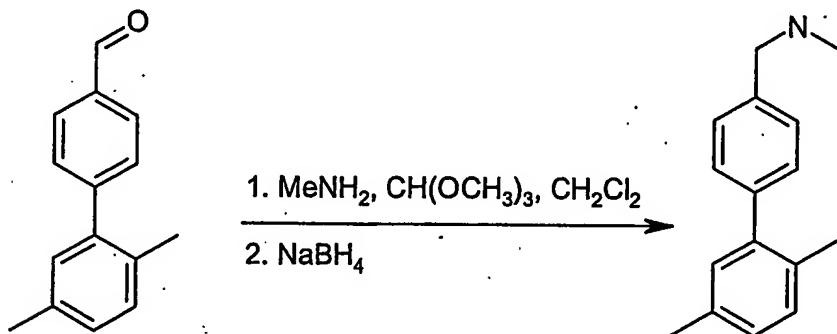
Compound 27a: 2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde



Following General Procedure 1, 2-iodo-1,4-dimethyl-benzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.67 g, quantitative). The crude material was of sufficient purity (>90%) to be used in the subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 10.06 (s, 1H), 7.92 (dd, $J=1.8$ Hz, $J=8.2$ Hz, 2H), 7.49 (dd, $J=1.6$ Hz, $J=8.4$ Hz, 2H), 7.18 (d, $J=7.6$ Hz, 1H), 7.12 (d, $J=8.4$ Hz, 1H), 7.05 (s, 1H), 2.36 (s, 3H), 2.23 (s, 3H).

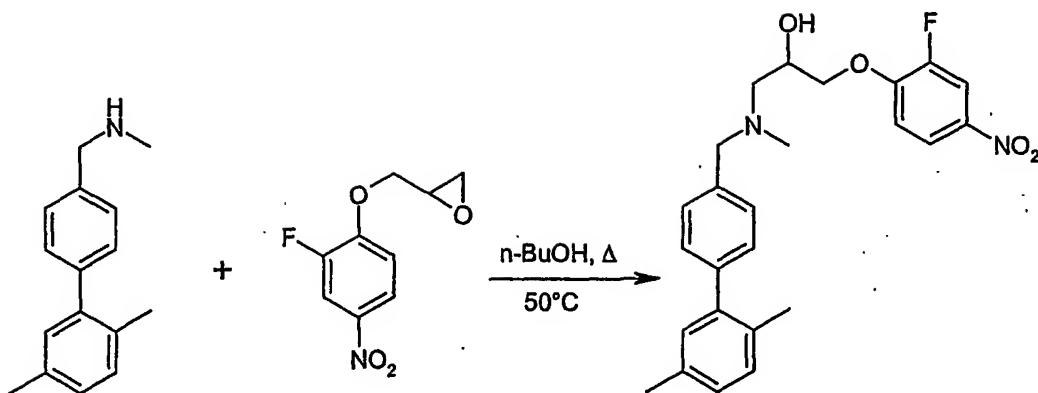
10

Compound 27b: *N*,*N*,*N*'-Trimethyl-[1,1'-biphenyl]-4-methanamine

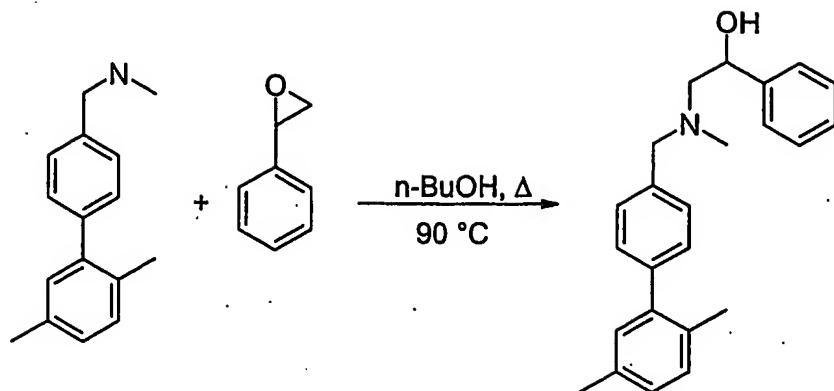


2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.263 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.203 g, 80%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. MS (ESI) ($\text{M}+\text{H}$) $^+ = 226$.

20 Compound 27c: 1-[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.068 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25–40% CH₃CN in H₂O) to provide the title compound (0.056 g, 34%) as its TFA salt. This material was lyophilized from H₂O/CH₃CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 8.08-10.00 (br m, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 7.27 (br s, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.96 (s, 1H), 4.61, (br s, 0.5H), 4.46 (br s, 2H), 4.28-4.18 (overlapping br d at 4.26 and br s at 4.18, *J*=15.2 Hz, 2.5H), 3.54-3.22 (br d at 3.52, br s at 3.39, and br s at 3.22, *J*=12.4 Hz, 2H), 2.98-2.91 (overlapping br s at 2.98 and br s at 2.91, 3H); 2.29 (s, 3H), 2.15 (s, 3H). MS (ESI) (M+H)⁺ = 439. Anal. Calcd for C₂₅H₂₇FN₂O₄ + 0.4 H₂O + 1.2 TFA: C, 56.49; H, 5.02; N, 4.81. Found: C, 56.46; H, 5.01; N, 4.86.

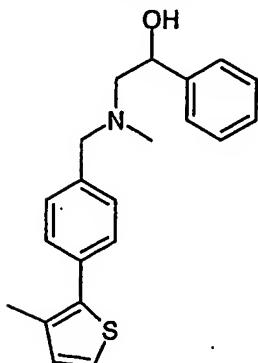


Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.32 mmol) and 2-phenyl-oxirane (0.038 g, 0.32 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC

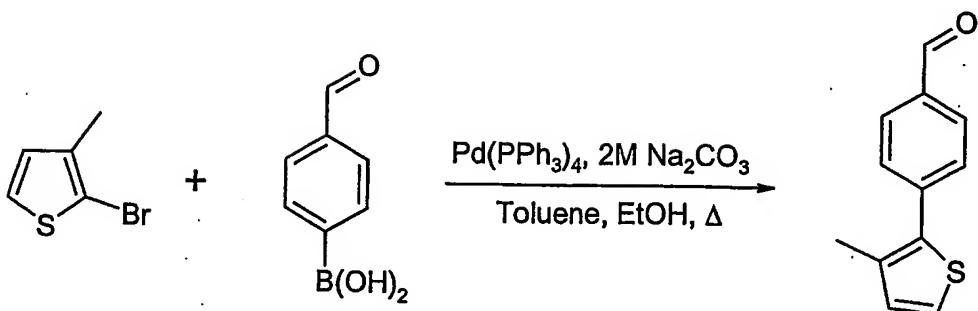
5 (gradient 25–40% CH₃CN in H₂O) to provide the title compound (0.033 g, 22%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained.

¹H-NMR (CD₃OD): δ 7.54 (br s, 2H), 7.40–7.31 (br m, 7H), 7.13 (d, *J*=8.0 Hz, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 6.98 (s, 1H), 5.08 (dd, *J*=3.6 Hz, *J*=10.8 Hz, 1H), 4.71 (br d, *J*=10.0 Hz, 0.5H), 4.44 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.41–3.16 (br d at 3.39, and br m, *J*=12.8 Hz for d, 2H), 3.03 (br s, 1.5H), 2.87 (br s, 1.5H), 2.29 (s, 3H), 2.16 (s, 3H). MS (ESI) (M+H)⁺ = 346. Anal. Calcd for C₂₄H₂₇NO + 0.6 H₂O + 1.0 TFA: C, 66.40; H, 6.26; N, 2.98. Found: C, 66.45; H, 6.16; N, 2.68.

15 Example 29: *α*-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol

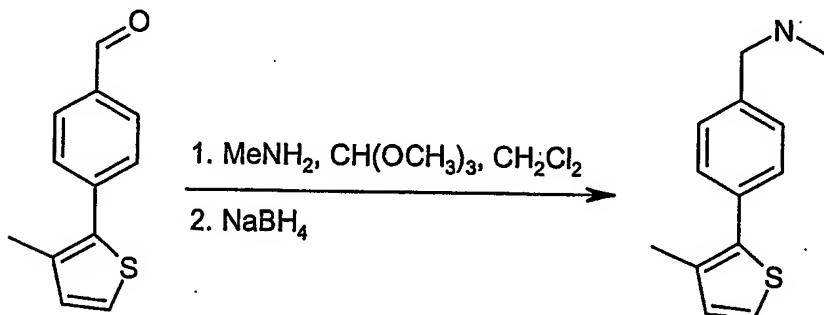


Compound 29a: 4-(3-Methyl-2-thienyl)-benzaldehyde



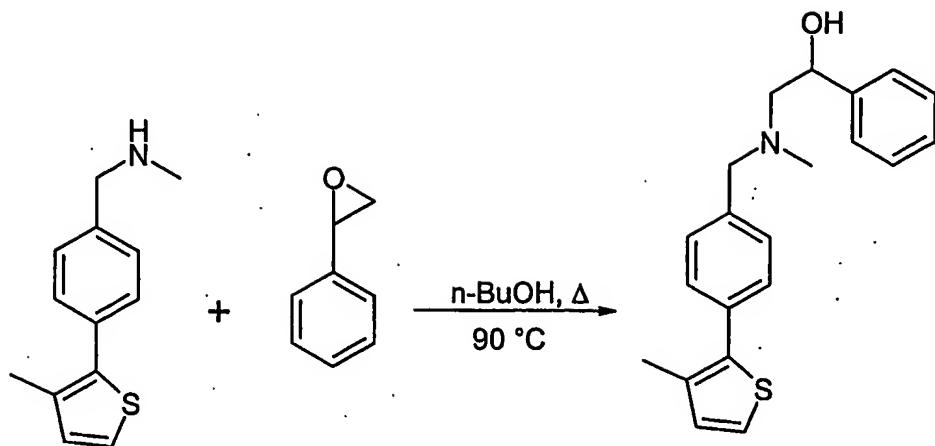
Following General Procedure 1, 2-bromo-3-methyl-thiophene (0.88 g, 4.95 mmol), 4-formylphenylboronic acid (1.11 g, 7.43 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.29 g, 0.25 mmol), and 2 M Na_2CO_3 (15 mL, 35 mmol) were combined. Following the usual work-up provided 5 the title compound (0.579 g, 58%). The crude material was of sufficient purity (>50%) to be used in subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 10.04 (s, 1H), 7.92 (d, $J=8.4$ Hz, 2H), 7.64 (d, $J=8.4$ Hz, 2H), 7.30 (d, $J=5.2$ Hz, 1H), 6.97 (d, $J=5.2$ Hz, 1H), 2.39 (s, 3H).

10 **Compound 29b: *N*-Methyl-4-(3-methyl-2-thienyl)-benzenemethanamine**



4-(3-Methyl-2-thienyl)-benzaldehyde (0.253 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.139 g, 57%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. $^1\text{H-NMR}$ (CDCl_3): δ 7.55 (d, $J=8.4$ Hz, 1H), 7.42 (d, $J=8.4$ Hz, 1H), 7.38-7.33 (overlapping d at 15 7.37, $J=8.4$ Hz, and d at 7.34, $J=8.4$ Hz, 2H), 7.18 (d, $J=5.2$ Hz, 1H), 6.91 (d, $J=5.2$ Hz, 1H), 3.77 (s, 2H), 2.47 (s, 3H), 2.32 (s, 3H). MS (ESI) ($\text{M}+\text{H}$) $^+ = 218$.

20 **Compound 29c: α -[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol**



Following General Procedure 5, *N*-methyl-4-(3-methyl-2-thienyl)-benzenemethanamine (0.109 g, 0.50 mmol) and 2-phenyl-oxirane (0.060 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified

5 by reverse phase HPLC (gradient 20-30% CH₃CN in H₂O) to provide the title compound (0.032 g, 14%) as its TFA salt. This material was lyophilized from H₂O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 10 2 diastereomeric salts was obtained. ¹H-NMR (CD₃OD): δ 7.62-7.57 (m, 4H), 7.42-7.33 (overlapping d at 7.33 and m, *J*=4.8 Hz for d, 6H), 6.96 (d, *J*=5.2 Hz, 1H), 5.12 (br s, 1H), 4.73 (br d, *J*=12.8 Hz, 0.5H), 4.45 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.43-3.18 (br d at 3.42, *J*=12.4 Hz, br d at 3.18, *J*=11.2 Hz, and br m, 2H), 3.04 (s, 1.5H), 2.88 (s, 1.5H), 2.33 (s, 3H). MS (ESI) (M+H)⁺ = 338. Anal. Calcd for C₂₁H₂₃NOS + 0.8 H₂O + 1.1 TFA: C, 58.38; H, 5.43; N, 2.93. Found: C, 58.48; H, 5.41; N, 2.93.

15

EXAMPLES 30- 132

Additional exemplary compounds were prepared according to the general procedures and the examples described above. Mass spectra of these compounds were obtained to confirm the formation of these compounds. These exemplary compounds and the 20 mass spectrum results thereof are listed in Table 2 below.

Table 2

Example No.	Compound Name	MS (ESI) (M+H) ⁺
30	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[methyl [2'-trifluoromethyl][1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	472
31	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[(2'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol	434
32	β -Ethoxy-N-methyl-N- [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]benzeneethanamine	414
33	N-Methyl-N- [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]glycylglycine, ethyl ester	409
34	N-Ethyl-2-[methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]acetamide	351
35	α -[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-7-[2-(trifluoromethyl)phenyl]-2(1H)-isoquinolineethanol	491
36	α -[Methyl (2,2',5'-trimethyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol	360
37	1-[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
38	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	466
39	1-[[[2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	479
40	1-[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	451
41	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile	436
42	1-[[[2'-Chloro-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
43	1-[[[5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
44	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl (2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol	456

Example No.	Compound Name	MS (ESI) (M+H) ⁺
45	α -[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]methyl]benzenemethanol	358/360
46	4'-[[2-Hydroxy-2-phenylethyl)methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile	343
47	α -[[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366/368
48	α -[[Methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	400
49	α -[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	420/422
50	4'-[[2-Hydroxy-2-phenylethyl)methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	373
51	α -[[[(2'-Fluoro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	336
52	α -[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	386/388/390
53	Methyl 3-[4-[[2-hydroxy-2-phenylethyl)methylamino]methyl]phenyl]-2-thiophenecarboxylate	382
54	α -[[Methyl[[2'-(1-methylethoxy)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	376
55	α -[[[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	362
56	α -[[Methyl[[2'-(2-propenyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	358
57	α -[[[(2'-Cyclopentyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	386
58	α -[[Methyl[[5'-methyl-2'-(1-methylethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	374
59	α -[[[(2'-Methoxy-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	362
60	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	493

Example No.	Compound Name	MS (ESI) (M+H) ⁺
61	α -[[[5-(4-Bromophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	386/388
62	α -[[[5-(4-Chlorophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	342
63	α -[[Methyl[[5-[3-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376
64	Methyl 3-[5-[(2-hydroxy-2-phenylethyl)methylamino]methyl]-2-furanyl]-2-thiophenecarboxylate	372
65	α -[[Methyl[[4-(3-pyridinyl)phenyl]methyl]amino]methyl]benzenemethanol	319
66	1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-[4-(1,1-dimethylethyl)phenoxy]-2-propanol	438
67	1-(4-Chlorophenoxy)-3-[methyl[[2'-trifluoromethyl][1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	450
68	1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-phenoxy-2-propanol	416
69	1-[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	423
70	α -[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzeneethanol	400
71	1-(1,1-Dimethylethoxy)-3-[methyl[[2'-trifluoromethyl][1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	396
72	Methyl 2-hydroxy-2-methyl-3-[methyl[[2'-trifluoromethyl][1,1'-biphenyl]-4-yl]methyl]amino]propanoate	382
73	(β ¹ S)- β -[[2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-cyclohexanepropanol	372
74	1-(4-Chlorophenoxy)-3-[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-propanol	422
75	1-[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	388
76	1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	408

Example No.	Compound Name	MS (ESI) (M+H) ⁺
77	1-Phenoxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	442
78	1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(3,4-dichlorophenoxy)-2-propanol	476
79	1-[(1,1'-Biphenyl)-4-ylmethyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	419
80	1-[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	433
81	1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	453
82	1-(4-Nitrophenoxy)-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	487
83	(α^1S)- α -[[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	358
84	(α^1S)- α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	378
85	(2R)-3-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-hydroxypropyl butanoate	402
86	(2R)-2-Hydroxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propyl butanoate	436
87	Methyl 2-hydroxy-2-methyl-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate	408
88	1-(3-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	479
89	1-(4-Iodophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	542
90	1-(3-Fluorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	434
91	Ethyl 4-[2-hydroxy-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propoxy]-benzenecarboximidate	487
92	1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-fluoro-4-nitrophenoxy)-2-propanol	445

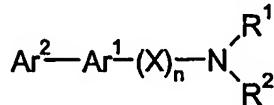
Example No.	Compound Name	MS (ESI) (M+H) ⁺
93	1-[[[2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	445
94	1-[[[2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	427
95	1-[[[2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol	376
96	1-[[[2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	421
97	<i>N,N</i> -Diethyl-4-[3-[[5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]-3-methoxybenzamide	509
98	Ethyl 4-[3-[[5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	451
99	4-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]- <i>N,N</i> -diethyl-3-methoxybenzamide	579
100	2-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzamide	493
101	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-methoxyphenoxy)-2-propanol	480
102	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(1 <i>H</i> -indol-5-yloxy)-2-propanol	489
103	Ethyl 4-[3-[[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	521
104	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol	450
105	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
106	2-Fluoro- α -[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol	404

Example No.	Compound Name	MS (ESI) (M+H) ⁺
107	α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	370
108	α -[[[(2'-Chloro-6'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366
109	α -[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	364
110	4-Chloro- α -[[[(2',5'-dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	380
111	α -[[Methyl[[4-(4-methyl-3-thienyl)phenyl]methyl]amino]methyl]benzenemethanol	338
112	1-(2-Fluoro-4-nitrophenoxy)-3-[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	497
113	1-[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	479
114	1-(4-Fluorophenoxy)-3-[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	452
115	α -[[[(3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	404
116	2-Fluoro- α -[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	422
117	4-Chloro- α -[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	438
118	1-[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
119	1-[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
120	1-[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	468
121	α -[[[(2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	420

Example No.	Compound Name	MS (ESI) (M+H) ⁺
122	α -[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	438
123	4-Chloro- α -[[[2-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	454
124	α -[[[(2-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	352
125	1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	475
126	1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	457
127	1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	430
128	α -[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	382
129	α -[[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	400
130	4-Chloro- α -[[[(2'-chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	416
131	α -[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-4-(trifluoromethyl)benzenemethanol	450
132	α -[[Methyl [5-[2-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:



5

I

wherein

Ar^1 is arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is separated from a ring atom of Ar^1 connected to X by at least one atom;

10 Ar^2 is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

n is 0 or 1;

X is a divalent group that separates groups connected thereto by one or two atoms;

15 R^1 is a monovalent C_{1-20} group comprising one or more heteroatoms selected from S, O, N and P;

R^2 is hydrogen, C_{1-10} alkyl, C_{1-10} acyl, substituted C_{1-10} acyl, substituted C_{1-10} alkyl, C_{1-10} alkylene, or substituted C_{1-10} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1 .

20 2. A compound of claim 1, wherein

Ar^1 is an arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is separated from a ring atom of Ar^1 connected to X by at least one atom;

25 Ar^2 is an aryl, heteroaryl, substituted aryl or substituted heteroaryl;

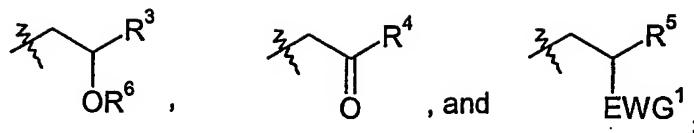
X is $-\text{CH}_2-$, or $-\text{CH}_2-\text{CH}_2-$;

30 R^2 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1 .

3. A compound of claim 2,

35 wherein

R^1 is selected from:



wherein R^3 is optionally hydrogen, substituted C_{1-10} alkyl, optionally substituted C_{5-12} aryl, optionally substituted C_{3-10} heteroaryl, optionally substituted 5

aryloxy- C_{1-6} alkyl, optionally substituted heteroaryloxy- C_{1-6} alkyl;

R^4 and R^5 are, independently, hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted C_{5-12} aryl, optionally substituted C_{3-10} heteroaryl, amino group, $-NHC(=O)-O-R^7$, or $-NHC(=O)-R^7$, wherein R^7 is C_{1-6} alkyl or aryl;

R^6 is hydrogen, optionally substituted C_{1-6} alkyl, or optionally substituted aryl;

10 and

EWG^1 is an electron withdrawing group.

4. A compound according to claim 1, wherein

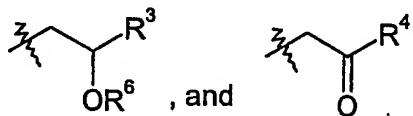
Ar^1 is optionally substituted *para*-phenylene, optionally substituted six-15 membered *para*-heteroarylene, or optionally substituted monocyclic five-membered *meta*-heteroarylene;

Ar^2 is optionally substituted phenyl, or optionally substituted monocyclic five or six-membered heteroaryl;

X is $-CH_2-$, or $-CH_2-CH_2-$;

20 R^2 is C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1 .

R^1 is selected from:



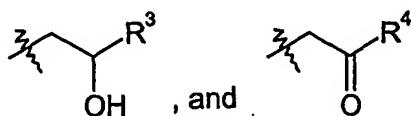
wherein R^3 is optionally substituted C_{1-6} alkyl, optionally substituted phenyl, 25 optionally substituted phenoxy-methyl;

R^4 is, independently, optionally substituted C_{1-6} alkyl, optionally substituted phenyl, amino, $-NHC(=O)-O-R^7$, or $-NHC(=O)-R^7$, wherein R^7 is C_{1-6} alkyl or phenyl;

and

R^6 is hydrogen, methyl or ethyl.

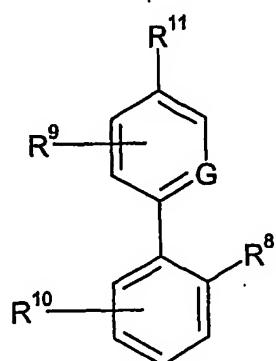
5. A compound according to claim 1, wherein
 Ar¹ is *para*-phenylene or *para*-pyridylene;
 Ar² is a phenyl *ortho*-substituted with an electron withdrawing group, or a
 5 thiienyl *ortho*-substituted with an electron withdrawing group;
 X is -CH₂-;
 R² is methyl.
 R¹ is selected from:



10 wherein R³ is optionally substituted phenyl, or optionally substituted phenoxy-methyl; and
 R⁴ is -NHC(=O)-O-R⁷, wherein R⁷ is C₁₋₆alkyl.

6. A compound according to claim 5, wherein
 15 Ar² is a phenyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-CH(CH₃)₂,
 -CF₃, -NO₂, or -CN; or thiienyl *ortho*-substituted with -Cl, -F, -OMe, -OEt,
 -O-CH(CH₃)₂, -CF₃, -NO₂, -CN, wherein said *ortho*-substituted Ar² is optionally
 further substituted at its non-*ortho* position; and
 R³ is phenyl, substituted phenoxy-methyl or substituted phenyl.

20 7. A compound of formula II, or a pharmaceutically acceptable salt thereof:



II

wherein

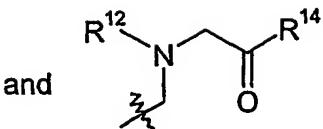
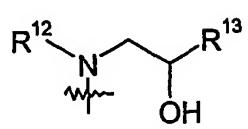
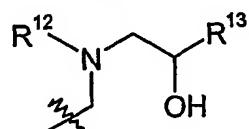
G is N or CH ;

R^8 is selected from $-H$, $-CH_3$, $-CF_3$, $-NO_2$ and $-CN$;

R^9 is selected from $-H$ and $C_{1-3}alkyl$;

5 R^{10} is selected from $-H$ and $C_{1-3}alkyl$; and

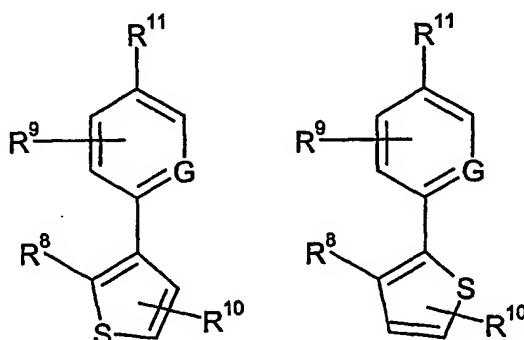
R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxyethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is $C_{1-6}alkyl$.

10

8. A compound of formula III or IV, or a pharmaceutically acceptable salt thereof:



III

IV

15 wherein

G is N or CH ;

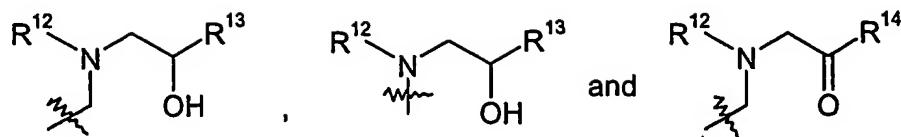
R^8 is selected from $-H$, $-CH_3$, $-CF_3$, $-NO_2$ and $-CN$;

R^9 is selected from $-H$ and $C_{1-3}alkyl$;

R^{10} is selected from $-H$ and $C_{1-3}alkyl$; and

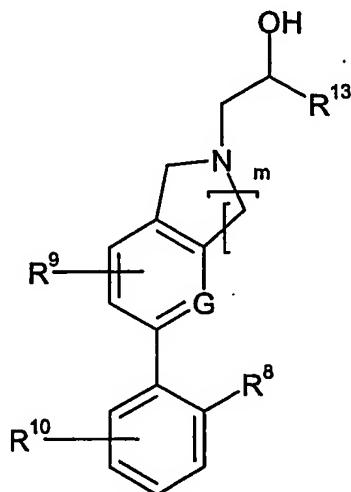
20 R^{11} is selected from

86



wherein R¹² is H or methyl, R¹³ is phenyl or substituted phenoxyethyl, R¹⁴ is -NHC(=O)OR¹⁵, wherein R¹⁵ is C₁₋₆alkyl.

5 9. A compound of formula V, or a pharmaceutically acceptable salt thereof:

**V**

wherein

10 G is N or CH;
 m is 1 or 2;
 R⁸ is selected from -H, -CH₃, -CF₃, -NO₂ and -CN;
 R⁹ is selected from -H and C₁₋₃alkyl;
 R¹⁰ is selected from -H and C₁₋₃alkyl; and
 15 R¹³ is phenyl or substituted phenoxyethyl.

10. A compound is selected from:

α-[[Methyl[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol;

α-[[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α -[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

5 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol;

α -[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

10 Ethyl [[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]-acetyl]carbamate;

3,4-Dihydro- α -phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol;

15 α -[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol;

α -[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol;

20 α -[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol;

(α^1S)- α -[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

(α^1R)- α -[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

α -[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

5 N -(2-Hydroxy-2-phenylethyl)- N -[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide;

N -(2-Hydroxy-2-phenylethyl)- N -methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide;

β -Methoxy- N -methyl- N -[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-benzeneethanamine;

10 3,4-Dihydro- α -phenyl-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

α -[[Methyl[[5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl]methyl]amino]methyl]-benzenemethanol;

 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

15 1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-(4-nitrophenoxy)-2-propanol;

 1-[[2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

20 α -[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

 4-Chloro- α -[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methyl]methylamino]methyl]-benzenemethanol;

 1-[[2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

α -[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α -[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol;

5 1-[4-(1,1-Dimethylethyl)phenoxy]-3-[methyl][2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-[4-(1,1-Dimethylethyl)phenoxy]-3-[[2'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol;

10 β -Ethoxy-N-methyl-N-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]benzenethanamine;

N-Methyl-N-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]glycylglycine, ethyl ester;

N-Ethyl-2-[methyl][2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]acetamide;

15 α -[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-7-[2-(trifluoromethyl)phenyl]-2(1H)-isoquinolineethanol;

α -[[Methyl[(2,2',5'-trimethyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol;

20 1-[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile;

1-[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

4-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile;

5 1-[[(2'-Chloro-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

10 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl][(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol;

α -[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]methyl]benzenemethanol;

4-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile;

15 α -[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α -[[Methyl|[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

20 α -[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

4-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile;

α -[[[(2'-Fluoro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α -[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

Methyl 3-[4-[[[2-hydroxy-2-phenylethyl)methylamino]methyl]phenyl]-2-thiophenecarboxylate;

5 α -[[[Methyl[[2'-(1-methylethoxy)[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol;

α -[[[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

10 α -[[[Methyl[[2'-(2-propenyl)[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol;

α -[[[(2'-Cyclopentyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α -[[[Methyl[[5'-methyl-2'-(1-methylethyl)[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol;

15 α -[[[(2'-Methoxy-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol;

20 α -[[[[5-(4-Bromophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol;

α -[[[[5-(4-Chlorophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol;

α -[[[Methyl[[5-[3-(trifluoromethyl)phenyl]-2-furanyl)methyl]amino]methyl]benzenemethanol;

Methyl 3-[5-[(2-hydroxy-2-phenylethyl)methylamino]methyl]-2-furanyl]-2-thiophenecarboxylate;

α -[[Methyl[[4-(3-pyridinyl)phenyl]methyl]amino]methyl]benzenemethanol;

1-[[2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-[4-(1,1-dimethylethyl)phenoxy]-2-propanol;

1-(4-Chlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-phenoxy-2-propanol;

10 1-[[2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

α -[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzeneethanol;

1-(1,1-Dimethylethoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

Methyl 2-hydroxy-2-methyl-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate;

(β^1S)- β -[[2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-cyclohexanepropanol;

20 1-(4-Chlorophenoxy)-3-[[2'-methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-propanol;

1-[[2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol;

1-Phenoxy-3-[2-propenyl][[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

5 1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(3,4-dichlorophenoxy)-2-propanol;

1-[[[1,1'-Biphenyl]-4-ylmethyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

10 1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

1-((4-Nitrophenoxy)-3-[2-propenyl][[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

15 (α^1S)- α -[[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol;

(α^1S)- α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol;

20 (2R)-3-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-hydroxypropyl butanoate;

(2R)-2-Hydroxy-3-[2-propenyl][[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propyl butanoate;

Methyl 2-hydroxy-2-methyl-3-[2-propenyl][[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate;

1-(3-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-(4-Iodophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

5 1-(3-Fluorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

Ethyl 4-[2-hydroxy-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propoxy]-benzenecarboximidate;

10 1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-fluoro-4-nitrophenoxy)-2-propanol;

1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

15 1-[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol;

1-[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

N,N-Diethyl-4-[3-[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]-3-methoxybenzamide;

20 Ethyl 4-[3-[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate;

4-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]-N,N-diethyl-3-methoxybenzamide;

5 2-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzamide;

1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(3-methoxyphenoxy)-2-propanol;

10 1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(1*H*-indol-5-yloxy)-2-propanol;

Ethyl 4-[3-[[[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate;

15 1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-phenoxy-2-propanol;

2-Fluoro- α -[[methyl][[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

20 α -[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobzenemethanol;

α -[[[(2'-Chloro-6'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α -[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobzenemethanol;

4-Chloro- α -[[[(2',5'-dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α -[[Methyl[[4-(4-methyl-3-thienyl)phenyl]methyl]amino]methyl]benzenemethanol;

5 1-(2-Fluoro-4-nitrophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol;

1-[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-(4-Fluorophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol;

10 α -[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]benzenemethanol;

2-Fluoro- α -[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]benzenemethanol;

15 4-Chloro- α -[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]benzenemethanol;

1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

20 1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol;

α -[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl)methyl]methylamino]benzenemethanol;

α -[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]-2-fluorobenzenemethanol;

4-Chloro- α -[[[2-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

5 α -[[[2-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

10 1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol;

α -[[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methyl]methylamino]methyl]benzenemethanol;

15 α -[[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol;

4-Chloro- α -[[[2'-chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

20 α -[[[2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-4-(trifluoromethyl)benzenemethanol;

α -[[Methyl[[5-[2-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol; and pharmaceutically acceptable salts thereof.

25 11. A compound according to any one of claims 1-10 for use as a medicament.

12. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the therapy of pain.

5 13. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the treatment of immune cancer.

14. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the treatment of multiple sclerosis, vision

10 impairment, Parkinson's disease, Huntington's chorea or Alzheimer's disease.

15. A pharmaceutical composition comprising a compound according to any one of claims 1-10 and a pharmaceutically acceptable carrier.

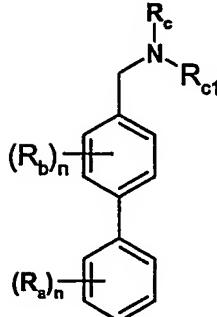
16. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-10.

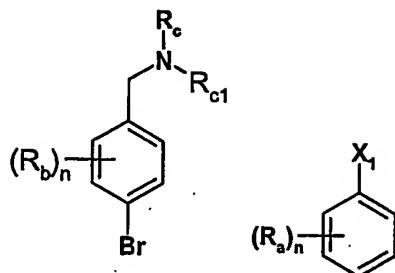
17. A method for preparing a compound of formula X,

20 X

comprising the steps of

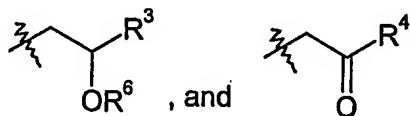
a) reacting a compound of formula IX with bis(pinacolato)diboron in the presence of $Pd(PPh_3)_4$; and



IXVI

b) reacting a product of step a) with a compound of formula VI to form the compound of formula X,

5 wherein R_a and R_b are independently selected from -H, C₁₋₆alkyl, -CF₃, -NO₂, and -CN; n is 1 or 2; R_c is selected from:



wherein R³ is optionally substituted phenyl, or optionally substituted phenoxy-methyl;

10 R⁴ is -NHC(=O)-O-R⁷, wherein R⁷ is C₁₋₆alkyl; and R_{c1} is -H or C₁₋₃alkyl.

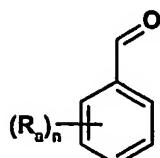
10

18. A process for preparing a compound of formula XIII,

XIII

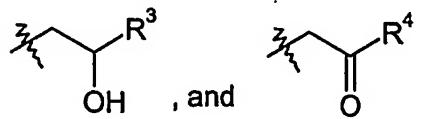
comprising the steps of:

a) reacting a compound of formula XI with R_dR_eNH; and

XI

b) reacting a product of step a) with $\text{NaBH}(\text{OAc})_3$ to form the compound of formula XIII,

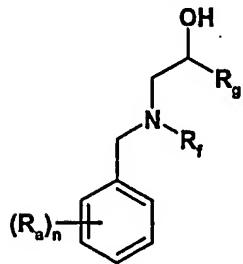
5 R_a is selected from optionally substituted aryl, optionally substituted heteroaryl;
 5 n is 1 or 2; R_d and R_e are independently selected from -H, C_{1-3} alkyl,



wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxy-methyl,

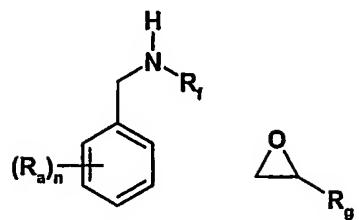
10 R^4 is $-\text{NHC}(=\text{O})-\text{O}-\text{R}^7$, wherein R^7 is C_{1-6} alkyl; wherein at least one of R_d and
 10 R_e contains an oxygen atom.

19. A method for preparing a compound of formula XV,

XV

comprising the step of:

15 reacting a compound of formula XII with a compound of formula XIV,



XI , **XIV** ,

wherein R_a is selected from optionally substituted aryl and optionally substituted heteroaryl; n is 1 or 2; R_f is -H or C_{1-3} alkyl; and R_g is optionally substituted phenyl or optionally substituted phenoxyethyl.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2003/002088

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 333/10, C07D 213/36, C07D 211/70, C07D 209/44, C07C 221/27,
 A61K 31/137, A61K 31/4035 A61K 31/4418, 31/451, 31/381, A61P 25/04
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemistry and Physics of Lipids, Volume 121, 2002, Sonya L. Palmer et al, "Review: Cannabinergic ligands", pages 3-19 --	1-19
A	Chemistry and Physics of Lipids, Volume 121, 2002, T. Philip Malan et al, "Review: Inhibition of pain responses by activation of CB2 cannabinoid receptors", pages 191-200 -- -----	1-19

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

5 April 2004

Date of mailing of the international search report

08-04-2004

Name and mailing address of the ISA/
 Swedish Patent Office
 Box 5055, S-102 42 STOCKHOLM
 Facsimile No. + 46 8 666 02 86

Authorized officer
 CAROLINA GÓMEZ LAGERLÖF/BS
 Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002088

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **1 6**
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet
2. Claims Nos.: **1-6**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see extra sheet
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002088

Box II.1

Claim 16 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

Box II.2

Present claims 1-6 relate to a large number of possible compounds. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds defined in claims 7-9.

THIS PAGE BLANK (USPTO)